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SAMSON WRIGHT

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OXFORD MEDICAL PUBLICATIONS

APPLIED PHYSIOLOGY

BY

SAMSON WRIGHT

M.D., M.R.C.P.

DEPARTMENT OF PHYSIOLOGY, MIDDLESEX HOSPITAL MEDICAL SCHOOL

WITH INTRODUCTION BY

SWALE VINCENT

M.D., LL.D., D.Sc., F.R.S.Ed. & Canada

PROFESSOR OF PHYSIOLOGY, UNIVERSITY OF LONDON

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DEDICATED

TO THE MEMORY OF

MY FATHER

INTRODUCTION

By SWALE VINCENT, M.D., D.Sc., LL.D., F.R.S.Ed. & Canada

PROFESSOR OF PHYSIOLOGY IN THE UNIVERSITY OF LONDON, MIDDLESEX HOSPITAL MEDICAL SCHOOL; EXAMINER IN PHYSIOLOGY TO THE CONJOINT BOARD

It will, I think, be admitted that there is a real need for a book of the kind furnished by Dr. Samson Wright.

It is now generally recognized that the science and art of medicine can only find a sure foundation on a sound knowledge of physiology. Applied Physiology may be regarded as a branch of pathology, inasmuch as it deals with the physiology of disease. Morbid processes have never received at the hands of pathologists the attention they deserve. Morbid anatomy and bacteriology have claimed most of the attention of workers, at any rate in this country.

The book should be specially valuable to students who have passed through their courses in Physiology and are entering upon their work in the wards and various departments of the hospital. A presentation of the facts of physiology in close connection with their medical bearings would in itself be of value, but Dr. Wright's book does more than this. It presents many facts and theories on the borderland of physiology and medicine which the student would have great difficulty in digging out for himself. For this and for the care and skill with which it has been done, many generations of students will have reason to be grateful.

The senior student of physiology will find that the use of this book, in conjunction with more formal text-books, will serve to concentrate his attention on those aspects of the subject which will be of importance to him in his later studies.

And the book appeals to a wider circle—those engaged in the practice of medicine. The day has gone by when a practitioner, however modest, can afford to declare that "he has forgotten his physiology." The present work will go far to remove any excuse from those who may find themselves in such a predicament.

PREFACE TO THE SECOND EDITION

In preparing the second edition I have subjected the text to a very thorough revision; many chapters have been rewritten, and considerable additions have been made to incorporate recent advances in the subject. Some of the more important new or enlarged sections are the following:

Hydrocephalus (p. 5), action of hypertonic saline on cerebro-spinal fluid (p. 6), evidence against conduction with decrement (pp. 15–17), Sherrington's humoral theory of reflex action (pp. 18–22), action of strychnine (p. 25), Adrian's work on action currents in sensory nerves (pp. 30–33), mode of action of dilator fibres in posterior nerve roots (pp. 34–35), stretch reflexes (pp. 51–55), peripheral mechanism of posture and discussion of rôle of sympathetic (pp. 55–57), fuller account of vestibular reflexes (pp. 61–64), Cannon's work on conditions governing adrenaline secretion (pp. 130–132), relation of hypothalamus to pituitary (p. 152), menstruation and the œstrous cycle (pp. 168–169), origin of constituents of milk and influence of diet (pp. 174–175), action of hæmostatics (p. 186), structure of bone marrow and development of blood in the light of the work of Sabin and her co-workers (pp. 189, 193, 206), pernicious anæmia and its dietetic control (p. 204), coronary circulation and coronary occlusion (pp. 242–244), hot wire sphygmograph (p. 250), vascular responses of skin, incorporating the recent work of Lewis and his co-workers, and a discussion of the "H"-substance (p. 293–298), lipoid nephrosis (p. 307), phosphagen (p. 355), interpretation of curves of gastric acidity (p. 385), Whitaker and Boyden's work on the gall-bladder (pp. 394–396), detailed account of the work of Mann and his co-workers on complete and partial extirpation of the liver (pp. 397–400), mode of action of insulin (p. 423), pellagra-preventing factor and isolation of vitamin B (p. 446), and new section on dietetics and composition of foodstuffs (p. 453). Considerations of space have deterred me from discussing other topics of equal or perhaps greater interest. The sections on coagulation of the blood, purpura, output of the heart, tissue oxidation, and fat metabolism have been completely rewritten, numerous other alterations and additions have been made, and about seventy new illustrations have been added. A coloured plate has been introduced to illustrate the development of the cells of the blood. In consequence the book has undergone enlargement to the extent of about one hundred pages. At the suggestion of Dr. Jung of Chicago a glossary of B.N.A. equivalents has been added, and the B.N.A. equivalents have also

been introduced at suitable points in the text within square brackets. I am indebted to Sir E. Sharpey-Schafer, Prof. Pembrey, and many correspondents at home and abroad for critical suggestions. It may be worth pointing out that the sections of the book which are mainly of clinical interest (*e.g.* pathological conditions of cerebro-spinal fluid, circus movement, cyanosis, intestinal intoxication, nephritis, and uræmia) could be safely neglected by the purely physiological reader.

I have to thank the following authors and publishers for permission to reproduce figures. Detailed acknowledgments are given in all cases in the text: Dr. Adrian, Dr. Izod Bennett, Dr. Bolton, Prof. Cannon, Dr. Cowdray, Prof. Cushing, Drs. Davis and Forbes, Drs. Doan, Cunningham, and Sabin, Prof. E. C. Dodds, Prof. Fraser, Dr. Fulton, Prof. Haldane, Dr. Harrison, Dr. Gordon Holmes, Dr. Krumbhaar, Sir Thomas Lewis, Dr. Lumsden, Prof. M'Dowall, Dr. M'Nee, the late Dr. Magnus, Prof. Meakins, Dr. Robson, Sir E. Sharpey-Schafer, Sir Charles Sherrington, Prof. Swale Vincent, Dr. Walshe, Prof. Weed, Prof. Wiggers, and Dr. Kinnier Wilson: the Editors of the *American Journal of Physiology*, the *Biochemical Journal*, the *British Medical Journal*, *Heart*, the *Journal of Physiology*, the *Lancet*, *Nature*, *Physiological Reviews*, the *Proceedings of the Royal Society*, the *Quarterly Journal of Experimental Physiology*, and the *Quarterly Journal of Medicine*: Messrs. Edward Arnold & Co., the Carnegie Institute, Cambridge University Press, Christophers, William Heinemann Ltd., Lea & Febiger, Longmans, Green & Co. Ltd., Macmillan & Co. Ltd., Shaw & Sons Ltd., and the Yale University Press.

I am indebted to Dr. Strickland Goodall for the original of Fig. 71. I must thank Sir E. Sharpey-Schafer and the Royal Society for the loan of clichés. Prof. Swale Vincent has kindly allowed me to reprint his introduction, and Mr. M. Kremer, B.Sc., has helped me in reading the proofs. My wife has been of the greatest assistance to me throughout, and I am particularly indebted to her for assistance with the index.

S. W.

Middlesex Hospital Medical School,
September 1928.

FROM THE PREFACE TO THE FIRST EDITION

This book is based on the various courses of lectures I have given both in the department of Physiology in the Middlesex Hospital Medical School, and to men working in the wards and the various departments of the Hospital. My aim has been to present clearly and concisely how the various functions of the body are performed. To economize space, no account is given, however, of the peripheral mechanism of vision or of hearing; otherwise, the ground is covered fairly completely. As the book is intended for medical readers, I have throughout laid emphasis on and devoted particular attention to those functions which are commonly deranged in disease. I have kept in view Dr. Haldane's dictum, that the aim of physiology is to consider how the internal environment of the body is kept constant in spite of continual alterations in the external environment. Throughout the text numerous cross references have been inserted which may help to clear up doubtful points, and are especially intended to impress on the reader that the subject must be considered as a co-ordinated and integrated whole, and that it does not deal with a series of isolated and independent organs and systems.

I have not attempted, in the more strictly applied sections of the book, to cover the ground completely, but I have selected from the mass of material available the problems of the greatest practical importance, and particularly those which are, perhaps, not so fully discussed in text-books of pathology or medicine.

I must confess to have paid some attention to the requirements of the various examining bodies. The physiological sections may prove useful to men reading for the second M.B. examination of the various Universities, and in particular I hope it will be helpful to men preparing for the Primary Fellowship examination of the Royal College of Surgeons. The applied sections may be found helpful by men reading for their final examinations, and perhaps even for the higher examinations of M.D. or M.R.C.P.

It seems to me unfortunate that in the teaching of physiology greater use is not made of the wealth of clinical material present in the wards of the Hospitals, which could readily be made available. The main facts of the physiology of the nervous system and the ductless glands, at any rate, could thus be clearly demonstrated; and the interest of the student would be aroused when he finds that he is considering in his physiological studies the same patients that he will have to deal with when doing his clinical

work. This is the method I have adopted whenever possible in this book. In considering the cerebellum, for example, a full account is given of the symptoms and signs of lesions to this structure in the *human* subject. This enables the student of physiology to draw his conclusions concerning the functions of the organ, and at the same time familiarizes him with the clinical aspects of disorders of the cerebellum. If a course of demonstrations such as I have suggested became an integral part of all courses in physiology, the medical student would enter on his clinical studies with a much sounder knowledge of the practically important parts of the subject, and with at least an elementary knowledge of medicine.

S. W.

Middlesex Hospital Medical School,
September 1926.

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GLOSSARY OF INTERNATIONAL (B.N.A.) ANATOMICAL NOMENCLATURE

Old Terminology.	B.N.A. Terminology.
Anterior primary division	Anterior ramus
Aqueductus Sylvii	Cerebral aqueduct
Auricle	Atrium
Auricular appendix	Auricula cordis
Auriculo-ventricular groove	Coronary sulcus
Canalis reuniens (auditory apparatus)	Ductus reuniens
Circle of Willis	Circulus arteriosus
Cisterna basalis	Cisterna interpeduncularis
Cisterna magna	Cisterna cerebello-medullaris
Clarke's column	Dorsal nucleus
Cranial nerves:	
Third	Oculomotor
Fourth	Trochlear
Fifth	Trigeminal
Descending nucleus	Nucleus of spinal tract
Descending root	Spinal tract
Sixth	Abducens
Seventh	Facial
Ninth	Glossopharyngeal
Eleventh (spinal-accessory)	Accessory
Twelfth	Hypoglossal
Crus cerebri	Cerebral peduncle
Discus proligerus	Cumulus
Fallopian tube	Uterine tube
Fissure of Rolando	Sulcus centralis
Foramen of Luschka	Lateral aperture
Foramen of Magendie	Medial aperture
Foramen of Monro	Interventricular foramen
Ganglion of Scarpa	Vestibular ganglion
Gasserian ganglion	Semilunar ganglion
Graafian follicle	Vesicular ovarian follicle
Inferior corpora quadrigemina	Inferior colliculi
Ileo-cæcal valve	Valvula coli

Old Terminology.	B.N.A. Terminology.
Internal capsule, anterior limb	Internal capsule, frontal part
Internal capsule, posterior limb	Internal capsule, occipital part
Lateral fillet	Lateral lemniscus
Malpighian corpuscle (kidney)	Renal corpuscle
Malpighian corpuscle (spleen)	Splenic lymphatic nodule
Meckel's ganglion	Spheno-palatine ganglion
Mesial fillet	Mesial lemniscus
Midbrain	Mesencephalon
Nasal nerve	Naso-ciliary nerve
Nucleus accessory (auditory)	Ventral (auditory)
Nucleus, Deiters'	Lateral vestibular
Nucleus lenticular	Lentiform
Optic radiation	Thalamo-occipital radiation
Optic thalamus	Thalamus
Pacchionian bodies	Arachnoideal granulations
Parathyroid	Parathyreoid
Pars intermedia	Nervus intermedius
Peduncles of cerebellum :	
Inferior	Restiform body
Middle	Brachium pontis
Superior	Brachium conjunctivium
Peyer's patches	Aggregated lymphatic nodules
Pituitary body	Hypophysis
Posterior longitudinal bundle	Median longitudinal bundle
Posterior primary division	Posterior ramus
Spinal cord	Medulla spinalis
Superior corpora quadrigemina	Superior colliculi
Thyroid	Thyreoid
Tract :	Tract :
Comma	Interfascicular
Crossed pyramidal	Lateral cerebro-spinal
Direct (dorsal) cerebellar of Flechsig	Dorsal spino-cerebellar
Direct pyramidal	Anterior cerebro-spinal
Indirect (ventral) cerebellar of Gowers	Ventral spino-cerebellar
Of Burdach	Funiculus cuneatus
Of Goll	Funiculus gracilis
Of Lissauer	Postero-lateral
Olivo-spinal	Bulbo-spinal
Pyramidal	Cerebro-spinal
Tuberculum acusticum	Dorsal (auditory) nucleus
Valve of Heister	Spiral valve
Vas deferens	Ductus deferens
Vein of Galen	Internal cerebral vein
Ventral longitudinal bundle	Median longitudinal bundle

APPLIED PHYSIOLOGY

I

THE NERVOUS SYSTEM

THE CEREBRO-SPINAL FLUID

Anatomy — Composition — Formation — Flow — Absorption — Action of drugs — Relation to nerve centres—Papillœdema—Hydrocephalus—Hypotonic and Hypertonic saline — Functions — Loculation syndrome — Lumbar puncture — Lipiodol—Protein—Cells—Colloidal benzoin reaction—Fluid in disease.

Anatomy.—Examination of the cerebro-spinal fluid has become such an important routine of clinical medicine that it is essential to have a clear conception of its physiology and anatomy.

The central nervous system is enveloped by the meninges, which from without inwards are termed dura, arachnoid, and pia. In the skull the dura consists of an outer or endosteal layer which lines the cranial bones, and an inner or meningeal layer. The two are closely connected, except where they separate to enclose the venous sinuses. The endosteal layer ceases at the foramen magnum, and the spinal dura only represents the meningeal layer of the cerebral dura. The dura is separated from the vertebræ by the epidural space, containing loose areolar tissue and a plexus of veins. Structurally it consists of fibrous tissue lined by endothelium. Separating it from the arachnoid is the subdural space, which contains a very small amount of fluid resembling lymph. The dura ends at the lower border of the second sacral, the spinal cord at the lower border of the first lumbar vertebra. The spinal theca can therefore be punctured in the lower lumbar region without fear of injury to the cord.

The arachnoid is separated from the pia by a space of varying size called the subarachnoid space, which contains the cerebro-spinal fluid. The pia invests the nervous substance very closely. The arachnoid, however, does not dip into the sulci or fissures (with the exception of the longitudinal sulcus), and invests the spinal cord quite loosely. There are also definite dilatations of the subarachnoid space called *cisternæ*. The cisterna magna [cerebello-medullaris] is found in the interval between the medulla and the under-surface of the cerebellum. The cisterna pontis lies on the ventral aspect of the pons and contains the basilar artery. The cisterna basalis [interpeduncularis] is formed by the arachnoid bridging across the interval between the tips of the temporal lobes, and contains the circle of Willis

[circulus arteriosus]. Prolongations of the subarachnoid space extend along the sheaths of the spinal and cranial nerves, particularly the optic (p. 5) and the auditory; by means of the last, communication is established with the perilymph of the internal ear. The rest of the cerebro-spinal fluid lies in the ventricles of the brain. Communication with the ventricles is established chiefly through the foramen of Magendie [medial aperture] in the middle line in the inferior part of the roof of the fourth ventricle and the foramina of Luschka [lateral apertures] at the extremities of the lateral recesses of this ventricle. As the arteries and veins enter and leave the brain substance they are surrounded by the perivascular spaces (of Virchow-Robin), which are continuous with the subarachnoid space and also with fine spaces which surround the nerve cells (see Fig. 1). Normally the

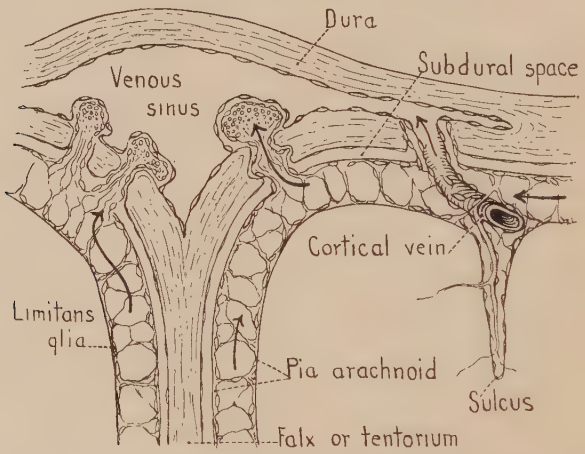


FIG. 1.—Diagram to show relations of Pia-arachnoid, the Arachnoid Villi, and the Cortical Veins to the Dural Sinuses. Note the clumps of cells (meningocytes [1]) lining the arachnoid villi, and the blood vessel coming from the brain substance surrounded by a continuation of the subarachnoid space. (Modified from Weed.) (H. Cushing, *Intracranial Physiology and Surgery*, 1926.)

flow along these perivascular spaces is outwards to the subarachnoid space, and they serve to remove waste products resulting from cell activity.

Composition.—Normal cerebro-spinal fluid is clear, colourless, and alkaline in reaction [2]; it consists mainly of water and contains the inorganic con-

[1] *Meningocytes.* Beside the flattened epithelial lining of the subarachnoid space, clumps of specialized cells called meningocytes are found scattered throughout the space, particularly in association with the arachnoid villi. These cells have the same staining reactions as those of the reticulo-endothelial system (p. 200), and have marked phagocytic powers, readily ingesting foreign substances. This is particularly well seen if laked blood is injected into the subarachnoid space: the meningocytes enlarge, become vacuolated, and detach themselves from their moorings to become free "macrophages" and take up free hæmoglobin, which they apparently convert into bile pigment, because this substance can be demonstrated in the cerebro-spinal fluid after a blood extravasation. (Cushing.)

[2] Sp. gr., 1004 to 1006.

stituents of the plasma in the same concentration. It contains very little protein, averaging 0·02 per cent., about equally distributed between albumin and globulin. The chloride content (expressed as NaCl) is very constantly 0·73 to 0·75 per cent. The glucose varies between 0·05 and 0·08 per cent. A few cells are found resembling lymphocytes, and their number does not exceed 5 per c.mm. of fluid. The fluid in the ventricles is probably non-albuminous and free from cells. Possibly the protein and cells are added to the fluid in the subarachnoid space by exudation from the meningeal blood-vessels. The total volume of the cerebro-spinal fluid is 100 to 150 c.cm. When free escape is allowed to the exterior, the amount formed daily may exceed 200 c.cm. and even reach 1 litre.

Formation of the Cerebro-Spinal Fluid.—There is no doubt that it is formed by the choroid plexuses, which are highly vascular fringes projecting into the cavity of all the ventricles. They are largest in the lateral ventricles. These vascular tufts are covered by a layer of epithelial cells which is a modification of the ependymal lining of the ventricles. The cerebro-spinal fluid passes from the lateral ventricles through the foramina of Monro [inter-ventricular foramina] into the third ventricle, aqueductus Sylvii [cerebral aqueduct], and fourth ventricle, and out through the foramina of Luschka and of Magendie into the subarachnoid space, both cerebral and spinal. There is considerable evidence, both experimental and clinical, in support of these statements.[1]

1. Experimentally, if a catheter is introduced into the third ventricle, a continuous flow of fluid is obtained. On occluding the aqueductus Sylvii the lateral ventricles become greatly distended from retained fluid, the condition being called *internal hydrocephalus*. Clinically, tumours of the brain stem obstructing the aqueductus Sylvii produce identical effects.

2. Unilateral hydrocephalus results when one foramen of Monro is occluded. If the corresponding choroid plexus is coincidentally extirpated the ventricle remains collapsed.

3. Obstruction of the foramina of Magendie and Luschka results in distension of the whole ventricular system. This may result from the more chronic sclerosing forms of meningitis—like the meningococcal and syphilitic—which chiefly affect the base of the brain, and also follows displacement of the brain in the later stages of cerebral tumour (p. 5).

Whether the cerebro-spinal fluid is formed as a result of secretion or simple filtration is undecided. As already mentioned, many of the constituents of the plasma are present in the cerebro-spinal fluid in about the same proportions. A rise in the glucose or urea content of the plasma is at once reflected in the fluid. Certain poisons like alcohol are similarly allowed to diffuse through, while the colloids are excluded. These facts suggest that the process is one of filtration. On the other hand, we find that substances like sodium iodide or sodium nitrate are held back, and that bile pigment does not enter the cerebro-spinal fluid from the general circulation (except in traces) even in deep jaundice. It therefore appears that the cells of the choroid plexus exert some selective activity over what substances are allowed to diffuse into the cerebro-spinal fluid. Drugs like pilocarpine may modify

[1] Dandy and Blackfan, *Amer. Journ. Child. Dis.*, 1914, vol. viii. pp. 406–482 ; Dandy, *Ann. Surgery*, 1919, vol. lxx. p. 129.

the activity of the cells of the choroid plexus and thus produce an increased formation of cerebro-spinal fluid.[1]

Absorption.—Most of the fluid is absorbed into the venous sinuses, though a little may pass into the perivascular spaces. Weed injected into the subarachnoid space of the living animal a solution of potassium ferrocyanide and iron ammonium citrate in isotonic saline, at a pressure of about 150 mm. H_2O. The nervous system and meninges were removed and fixed in acid solution which precipitated the salts as Prussian blue. Histological examination revealed the path taken by the injected material. The spinal and basilar portions of the subarachnoid space filled rapidly ; the cerebral part only after an interval of some hours. The dye could be seen passing through the arachnoid villi into the dural venous sinuses (and into the perivascular channels too if the animal were bled during the experiment). The arachnoid villi are numerous small finger-like processes which project through the dura into the venous sinuses, large and small, cortical and basilar, and form the principal path of absorption (see Fig. 1). The Pacchionian bodies [arachnoideal granulations] simply represent large villi, but they are few in number, are only present in the adult, and their importance is usually overestimated. Weed further found that colloids could be absorbed but slowly.

The process of absorption is one of diffusion. In cats the cerebro-spinal fluid pressure was about 120 mm. of water and exceeded the pressure in the venous sinuses by 5 to 50 mm. H_2O. Owing to this difference of pressure, fluid could pass into the veins. One would have thought that if the cerebro-spinal fluid pressure exceeded that in the veins, the latter would be compressed against the skull bones and be obliterated. The firm attachments of the dural layer forming the walls of the veins serve to prevent this. Weed has shown that at about the fifth week of embryonic life fluid begins to percolate through the remaining fragment of the roof plate overlying the fourth ventricle ; it finds its way into channels which are formed in the mesenchyme, and finally escapes by communications (which persist as the arachnoid villi) into the venous sinuses.

Clinical evidence suggests that important absorption of cerebro-spinal fluid is effected by the spinal veins too.

The normal pressure of the fluid depends on a balance between its rate of secretion and of absorption. The figures obtained in man in the recumbent position vary between 60 and 120 mm. H_2O. This is expressed clinically by the fluid issuing from a lumbar puncture needle at the rate of one drop per second. A rise of venous pressure such as follows coughing or crying will hinder absorption and so raise the pressure.

Relation of Cerebro-Spinal Fluid to Nerve Centres.—(i) *Cerebral Tumour.*—If there is any increase in the intracranial contents, as by a tumour of the cerebrum, additional room is made by expulsion of some cerebro-spinal fluid. Then the blood vessels are compressed and the gyri flattened, and gradually there is a general rise of pressure above the tentorium. This rise of pressure is transmitted to the prolongation of the subarachnoid space

[1] The action of different *drugs* on the secretion of the fluid has been investigated. It has been established that the volatile anæsthetics, especially ether, considerably increase the formation of cerebro-spinal fluid ; pilocarpine, as stated, may produce a similar but less marked effect. Substances like pituitrin, extracts of brain and choroid plexus, which have been alleged to produce some effect, are probably inert.

which surrounds the optic nerve. The first structures in the nerve to suffer from compression are the veins. Blood can still flow along the arteries and reach the optic disc, but its return is interfered with. In consequence, the veins at the nerve head become engorged and swollen, and fluid exudes from them at this point of least resistance. The resulting appearance, on opthalmoscopic examination, is termed *papillœdema*.

Pressure is then exerted on to the posterior fossa of the skull. The cerebellum is gradually driven into and through the foramen magnum, and fills this aperture like a cork. The disarrangement of the structures probably blocks the foramina of Magendie and Luschka, and impedes the escape of fluid into the spinal canal, where we noted that important absorption may occur. It will be readily seen that a vicious circle is established. The fluid cannot escape from the ventricles and is not absorbed, so that hydrocephalus results. This further raises the intracranial pressure, wedges the cerebellum still more firmly into the foramen magnum, and the cerebral vessels are further compressed ; finally, death results from medullary anæmia.

(ii) *Hydrocephalus* (pathological accumulation of cerebrospinal fluid).—This may arise in three major ways (Cushing). (1) Occlusion of the *arachnoid villi*, through which the fluid is absorbed into the sinuses. Chronic hydrocephalus of high grade can be experimentally produced by the injection into the subarachnoid space of lamp black, which blocks the villi. Cushing believes that damage to, or maldevelopment of, these structures is the commonest cause of early or congenital hydrocephalus, which otherwise is unexplained. In these cases cannulæ inserted into the ventricle (through the anterior fontanelle) and into the lumbar theca show the same pressure and similar fluctuations with crying or straining. Up to 300 c.cm. of fluid may be removed, but is found to have reaccumulated in 24 hours ; this suggests that the portals of outflow are at fault. One would have expected the accumulated fluid to be near the site of obstruction, *i.e.* in the subarachnoid space ; but on the contrary it is found chiefly in the distended ventricles. Even if a large hole is made in the thin cortex which separates the ventricles from the subarachnoid space, the hydrocephalus still remains *internal* ; and the thin cortex is soon floated up again to the dura.

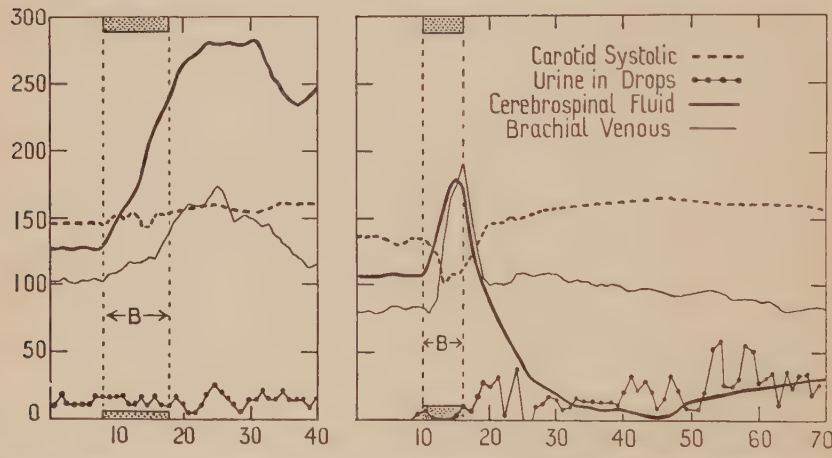
(2) Obstruction (from inflammation or tumour) of the *narrower* portions of the pathway : foramina of Monro, aqueductus Sylvii, roof of fourth ventricle, and the incisura tentorii. In the last case hydrocephalus is due to the fact that the cerebro-spinal fluid cannot escape to the supratentorial region, where the greater part of the process of absorption occurs.

(3) Very rarely the amount of fluid secreted may be in excess of that which can normally be removed : *e.g.* a case has been reported of *bilateral hypertrophy of the choroid plexuses* producing hydrocephalus. If the *vein of Galen* [internal cerebral vein] is obstructed close to its origin, internal hydrocephalus affecting all the ventricles results, presumably from engorgement of the choroid plexuses and overproduction of fluid.

(iii) *Injection of Saline Solutions.*[1]—The intravenous injection of large amounts of Ringer's solution causes a temporary rise of cerebro-spinal and venous pressure, both of which soon return to normal ; the injection of *hypotonic* saline (or distilled water) causes a transient increase of venous pressure, but a marked and prolonged rise of cerebro-spinal fluid pressure.

[1] Weed and Hughson, *Amer. Journ. Physiol.*, 1921, vol. lviii. p. 53.

(Fig. 2). This is probably due to differences in osmotic pressure causing passage of fluid into the brain substance and into the perivascular and the subarachnoid spaces. If *hypertonic* saline (*e.g.* 30 per cent. NaCl) is injected intravenously, it is found that the cerebro-spinal fluid pressure (after a sharp, brief rise) falls profoundly for a period of 2 to 4 hours, recovery usually occurring within 7 hours. This effect is independent of the arterial pressure, which shows variable changes, and of the venous pressure, which rises initially and then returns to about its original level (Fig. 3). There is marked shrinking of the brain substance : the convolutions become smaller and the sulci wider and deeper. The injection of 1 grm. NaCl per kg. body weight lowers the cerebro-spinal fluid pressure by about 8 cm. water ; 3·7 grm. per kg. of a 10 per cent. solution, or 1·7 grm. per kg. of a 20 per cent. solution of NaCl



Figs. 2 and 3.—Cat. Ordinates=mm. Ringer's solution (C.S.F. and venous pressures) or mm. mercury (carotid blood pressure) or drops of urine (in Fig. 2, 50 represents 10 drops, in Fig. 3, 50 represents 20 drops of urine). Abscissa=time in seconds. Fig. 2 during B—injection of 50 c.cm. distilled water. Fig. 3 during B—injection of 12 c.cm. 30 per cent. solution of NaCl. (Weed and Hughson, *Amer. Journ. Physiol.*)

intravenously may prove fatal if injected too rapidly. If 10 20 c.cm. of a 30 per cent. solution of NaCl are introduced into the duodenum or rectum of a cat the cerebro-spinal fluid pressure may fall by 26 cm. water and not be restored to normal for 17 to 48 hours ; if the fluid is introduced into the stomach the results are less certain ; saturated solutions of sodium sulphate give similar results, but are slower and less marked in their action. Speaking generally, we may say that hypertonic saline raises the osmotic pressure of the blood and causes fluid to pass from the brain substance and the cerebral spaces into the blood vessels.

Foley [1] has shown that hypertonic saline reverses the normal direction of cerebro-spinal fluid flow. Using Weed's Prussian blue method (p. 4), he introduced the ferro-cyanide and iron-ammonium citrate solution into the

[1] Foley, *Arch. Neurol. and Psychiat.*, 1921, vol. v. p. 744 ; *Arch. Surg.*, 1923, vol. vi. p. 587.

cisterna magna, and demonstrated that, after the intravenous injection of hypertonic saline, the dye passed freely into the perivascular spaces and into the blood vessels which they surround ; into the vessels which course through the subarachnoid space ; into the ventricular system and through the aqueductus Sylvii to the extremities of the frontal and occipital lobes. (Normally, even if the fluid is injected under a pressure of 400 mm. water, the dye does not penetrate beyond the aqueductus.) If a catheter connected to a manometer is introduced into the aqueductus Sylvii so as to obstruct it, it is found that the intravenous injection of hypertonic saline causes an immediate and profound fall of intraventricular pressure, *although the aqueductus is occluded* and the normal path of escape for the cerebro-spinal fluid is not available. If Weed's fluid is introduced through the catheter directly into the ventricles, and the experiment is repeated, the dye is found to pass through the cells of the choroid plexus into the contained capillaries. As the intraventricular pressure changes precede those in the subarachnoid space, it is obvious that fluid is being *absorbed* by the choroid plexuses (probably owing to differences of osmotic pressure), thus setting up a current of fluid into the ventricles.

Clinical Applications.—The raised intracranial pressure of *cerebral tumour* can be temporarily lowered by intravenous injection of hypertonic saline ; headache may be relieved for a few days and the swelling of the optic disc may be diminished. Cranial operations are made easier and safer, because the removal of the skull bones does not result in excessive bulging of brain substance such as usually occurs in cases with abnormally raised intracranial pressure.

Internal hydrocephalus benefits from this treatment to a marked degree because of the reversal of flow of the cerebro-spinal fluid and the absorption of the accumulated intraventricular fluid into the choroid plexuses and elsewhere as shown above.

Functions.—(1) The cerebro-spinal fluid serves as a fluid buffer. (2) It acts as a reservoir to regulate the contents of the cranium : if the volume of the brain or of the blood increases, cerebro-spinal fluid drains away ; if the brain shrinks, more fluid is retained. (3) It serves as a medium for nutrient exchanges in the nervous system.

"Loculation" Syndrome.—Ayer artificially obstructed the spinal subarachnoid space by injecting paraffin wax, which probably also compressed the spinal cord. Remarkable changes occur in the fluid below the level of the block. The protein content is greatly increased and the colour is now yellow. The exact cause of these changes is not known. Possibly the spinal veins which run longitudinally upwards are compressed. The veins become dilated and their internal pressure rises, and consequently blood corpuscles and plasma containing much protein exude. The hæmoglobin disintegrates and gives rise to a yellow pigment. Clinically chronic meningitis and tumours of the cord and its envelopes produce identical changes in the cerebro-spinal fluid—the so-called Froin or *loculation syndrome.* The protein is increased to 0·5 or 1 per cent., or even up to 4 per cent. The albumin and globulin are present in the same proportions as in blood. The fluid coagulates spontaneously, probably owing to the presence of fibrinogen. The yellow coloration is termed *xanthochromia.* The cell count is normal, except in the syphilitic cases. The only essential feature of the syndrome is the raised protein content above 0·5 per cent. (In inflammatory lesions of

the meninges the increased permeability of the blood vessels permits the exudation of fluid rich in protein.)

Lumbar Puncture is carried out by introducing a needle into the sub-arachnoid space below the termination of the spinal cord, usually between the spines of the fourth and fifth lumbar vertebræ.

INDICATIONS :

1. For diagnostic purposes.
2. To relieve raised intracranial pressure in meningitis, uræmia, etc.
3. Introduction of curative sera.
4. To produce spinal anæsthesia.

Lipiodol is a heavy liquid, opaque to the X-rays, which can be injected into the cisterna magna. Normally it drops by reason of its weight to the bottom of the spinal theca. If the subarachnoid space is obstructed by tumour or by adhesions, the lipiodol is held up at that point and its position can be demonstrated by the X-rays.

The significance of certain changes in the composition of the cerebro-spinal fluid will now be considered.

Protein.—The amount of protein is estimated by boiling with trichlor-acetic acid and comparing the turbidity produced with that of fluids containing known concentrations of protein.

If *globulin* is present in excessive amounts, the Nonne-Apelt reaction is obtained. On adding 1 c.cm. of cerebro-spinal fluid to 1 c.cm. of saturated ammonium sulphate solution a grey ring of precipitate appears at the junction of the two fluids.

The amount of protein is increased in all meningeal affections and is the expression of increased permeability of the inflamed blood vessels. A slight increase in protein, *i.e.* to 0·1 per cent. only, and a positive test for globulin are strongly suggestive of a syphilitic affection.

Cells.—An increase in the number of cells in the fluid is suggestive of inflammation.

Lymphocytosis usually occurs in acute infections, particularly in tubercular meningitis, lethargic encephalitis, acute anterior poliomyelitis, and in all syphilitic affections of the nervous system. In the last group the number of lymphocytes depends on the degree of meningeal involvement, and the number of cells may vary from 10 to 500 per c.mm.

Leucocytosis (polymorpho-nuclear) occurs in all pyogenic infections, *e.g.* meningococcus, pneumococcus, etc., and in some cases of tubercular meningitis. Large *mononuclear* cells appear in cases of tumours invading the meninges.

Glucose and **Urea** follow the level of these substances in the blood. The amount of glucose is high in diabetes, and the urea level is usually raised in uræmia. The amount of glucose is diminished in meningococcal meningitis, as the organism is thought to ferment the sugar. If the *chlorides* in the cerebro-spinal fluid rise above 0·75 per cent., renal insufficiency with salt retention is indicated; if they fall below 0·7 per cent., it is strong evidence of meningitis. The reason for this latter finding is not clear.

Colloidal Benzoin Reaction.—Normal cerebro-spinal fluid in any dilution added to a colloidal benzoin solution has no effect. In syphilis of the nervous system, incomplete flocculation (recorded as 1) or complete flocculation (2) may occur. Dilute the cerebro-spinal fluid $\frac{1}{10}$, $\frac{1}{20}$, $\frac{1}{40}$, $\frac{1}{80}$, $\frac{1}{160}$. In general paralysis of the insane the results obtained in the different dilutions

are 2, 2, 2, 2, 2 (*paretic* curve), *i.e.* complete flocculation occurs in all. In tabes and meningo-vascular syphilis the results are 1, 1, 2, 2, 1 (*luetic* curve), *i.e.* complete and incomplete flocculation occurs. A similar test can be carried out using a colloidal gold solution (Lange). The theory of the reaction is thought to be this: the albumin of the cerebro-spinal fluid normally checks flocculation; the excess of globulin present in syphilitic nervous disease overcomes this, and produces a precipitate.

The following tables (after Symonds) show the changes in the cerebro-spinal fluid in some important conditions:

	Normal Cerebro-Spinal Fluid.	Septic Meningitis.	Tubercular Meningitis.
Colour . .	Clear and colourless.	Turbid or purulent. Clot on standing.	Clear, thread-like coagulum on standing.
Protein . .	Average, 0·02 per cent.	Increased up to 0·2 per cent.	Increased to 0·2–0·3 per cent.
Sugar . .	0·08 per cent.	Diminished or absent.	Diminished, but not constantly.
Chlorides .	0·73–0·75 per cent.	Reduced to 0·7 or 0·6 per cent.	Reduced, often below 0·6 per cent.
Cells . .	1 to 4 lymphocytes per c.mm.	Increased. Hundreds of polymorphs.	Increased 10–400 per c.mm. Usually 75 per cent. lymphocytes.
Pressure .	1 drop per second.	Increased.	Increased.
		Causative organism present.	Tubercle bacilli may be present.

	General Paralysis.	Tabes.	Meningo-Vascular Syphilis.
Protein . .	0·05–0·1 per cent. Globulin reaction +.	0·03–0·08 per cent. Globulin reaction +.	0·03–0·08 per cent. Globulin reaction +.
Cells . . .	Up to 400 per c.mm. All lymphocytes.	10–80 c.mm. or more. All lymphocytes.	10–80 c.mm. All lymphocytes.
Wassermann reaction—			
Blood . .	Early, 75 per cent. +. Late, 100 per cent. +.	70 per cent. +.	80 per cent. +.
Cerebro-spinal fluid . .	All stages, 99 per cent. +.	70 per cent. +.	50 per cent. +.
Benzoin curve .	Paretic.	Luetic.	Luetic.

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STRUCTURE AND FUNCTION OF NERVE-REFLEX ACTION

Nerve cells — Nerve fibres — Degeneration and regeneration — Chromatolysis — Staining reactions—Functions—Recovery process in nerve—Varieties of fibres —All-or-none law—Heat production—Behaviour of narcotized nerve—Reflex action—Sherrington's "humoral" theory of excitation and inhibition—Recruitment and after-discharge—The final common path—Reciprocal innervation—Action of strychnine and tetanus toxin.

Structure of Nervous Tissue.—The term *neurone* is used to describe the nerve cell and its processes—dendrites and axon (nerve fibre). The nutrition of each neurone is independent.

Nerve Cells vary in size and shape in different parts of the body. The cytoplasm is fibrillated, the neurofibrils extending from the dendrites, through the substance of the cell, into the axon. Embedded in the cytoplasm are angular bodies—the Nissl granules—which stain deeply with basic dyes like methylene-blue. They are very deficient in many nerve cells. Their size and number vary with the physiological condition of the cell. Fatigue, the action of certain poisons, and section of the axis cylinder, cause the Nissl granules to disintegrate and disappear (*chromatolysis*). Chemically the granules consist of nucleo-protein and contain organically combined iron. The nucleus is large, shows a well-marked chromatin network and nucleoli. The dendrites branch repeatedly immediately they leave the cell, and contain Nissl granules.

Nerve Fibre arises from a part of the cell—the "axon hillock"—which is distinguished by the absence of Nissl granules. It runs as a rule for a considerable distance before branching.

Non-medullated fibres consist of a bundle of neurofibrils (the axis cylinder), surrounded by a limiting membrane—the neurolemma, within which is a little protoplasm containing nuclei.

Medullated fibres have surrounding the axis cylinder a white medullary sheath of a lipoid nature. It is highly refracting, and stains black with osmic acid. It is probably composed mainly of lecithine. The medullary sheath is constricted at regular intervals at the *nodes of Ranvier*. Outside the fibre is the homogeneous neurolemma. Midway between two nodes, an accumulation of nucleated protoplasm is found under the neurolemma.

In vertebrates it is thought that relatively undifferentiated tissue intervenes between one neurone and another, the junctional region being called the *synapse*, which has the following characters: (i) conduction is slow; (ii) fatigue readily occurs; (iii) conduction is in one direction only (nerve fibres conduct equally well in either direction); (iv) it is the site of action of certain drugs (*e.g.* strychnine); (v) it is probably responsible for certain features of reflex action such as summation and inhibition (cf. p. 18). In the case of the anterior horn cells at any rate, the afferent fibres end in

" pieds terminaux," or small varicosities which lie on the membrane which surrounds the nerve cell. The afferent neurone thus comes into very intimate relationship with the motor neurone. Sherrington suggests that in the terminals just mentioned the excitory and inhibitory substances may be liberated which are postulated in his " humoral " theory of reflex action (p. 18).

Degeneration and Regeneration of Nerve.—When a nerve fibre is divided, the part distal to the point of section undergoes degeneration. This process commences within twenty-four hours of the injury, and on the third day the fibre is incapable of conducting nervous impulses.

The histological changes in the peripheral end of the fibre are as follows :

1. The neurolemma thickens ; the subjacent nuclei enlarge and multiply, and the surrounding protoplasm increases in amount.

2. The medullary sheath breaks up into oily droplets of varying size. Chemically the process consists of the disintegration of the lecithine into its constituents, namely, two molecules of fatty acid (chiefly oleic acid), glycerol, phosphoric acid, and a nitrogenous base, choline. This change occurs simultaneously along the whole length of the fibre. The axis cylinder is split up into short lengths, and the broken ends of the fibres are enclosed in large fatty droplets. Eventually the remains of the original medullary sheath are removed by the phagocytic action of leucocytes in the surrounding tissue.

3. Ultimately all that is left of the fibre is the neurolemmal tube enclosing a mass of granular protoplasm containing many nuclei.

Chromatolysis occurs in the nerve cells giving rise to the fibres which have been divided. The changes begin within forty-eight hours of section of the nerve, and reach their zenith in fifteen to twenty days. They may be studied by dividing the hypoglossal nerve in animals.

Reaction Stage.—1. The Nissl granules break up into a fine dust. The process begins in the zone round the nucleus and spreads to the periphery of the cell and its processes. The dust may lose its staining reaction, and the cell appear colourless.

2. The cell swells from increased fluid content, loses its polygonal shape, and becomes rounded. The neurofibrils disappear first in the perinuclear zone and then elsewhere.

3. The nucleus increases in size and is displaced to the cell margin or to the base of one of the dendrites. On reaching the surface it becomes more oval, with the long axis parallel to the cell margin. It may be completely extruded, after which the cell atrophies and finally disappears.

The degree of chromatolysis depends on (i) distance of the section from the nerve cell ; (ii) nature of the section—if the nerve is forcibly torn, death of the cell results.

Reparative Stage.—This begins in twenty days and is completed in eighty days. The Nissl granules gradually reappear. The cell regains its normal size, and the nucleus returns to its central position. It must be remembered that repair of the cell may occur even if the axon does not regenerate.

Sensory Neurones.—1. If the peripheral axon of the posterior root ganglion is divided, the changes described above occur, but pass away more rapidly.

2. If the central axon is cut, the changes in the ganglion cells are

very meagre. Some cellular atrophy and neuroglial proliferation occur. Similarly, in tabes, where the central axons of the posterior nerve roots are damaged by syphilis, the ganglia show very slight changes.

Central Nervous System.—Very little attempt at repair occurs, and most of the cells go on to complete atrophy. This certainly applies to the cells of Betz, Clarke's column, and the red nucleus. The atrophy is more intense the nearer the lesion is to the cells.

Changes in sympathetic ganglia may occur, but are difficult to demonstrate owing to the normal sparseness of the Nissl granules.

Chromatolysis also occurs in *exhaustion*, *intoxications*, and *circulatory disturbances*, such as interference with the blood supply. If the blood supply is completely cut off, the cell rapidly becomes smaller, and the whole of the nucleus and protoplasm stain homogeneously with basic dyes. In *hyperpyrexia, e.g.* brief exposure to 109° F. or more prolonged exposure to 107° or 108° F., death of the cell and coagulation of its substance result.

Regeneration of Nerve.—If the cut ends of the nerve are brought into close and accurate contact, regeneration may occur from the central end of the nerve. Many bundles of neurofibrils sprout out and pass into and between the nucleated protoplasmic tubes forming the distal end of the nerve. Many of the fibrils branch, twist, or loop on themselves and are lost; only a proportion succeed in finding the distal end and growing along it. The growing end of the nerve consists of a bulbous swelling. The medullary sheath and the nodes of Ranvier develop later. The process of regeneration may take a few or many months to be completed, the time varying with the length of nerve to be regenerated. It is interesting to note that in the tadpole the axons develop as bulbous outgrowths from the primitive neuroblasts.

Staining Reactions of Nerve.—1. Normal nerve fibres stain black with osmic acid. The unsaturated fatty acids present in lecithine reduce the osmic acid to the lower black osmic oxide.

2. For accurate investigation of the white matter of the nervous system, the tissue must be fixed and hardened for a long time (weeks) in Müller's fluid (weak bichromate solution). To demonstrate areas of sclerosis or regions where the medullary sheaths have been destroyed, the *Weigert-Pal* stain is employed. The principle is to stain the whole section black with a modified hæmatoxylin stain. The stain is then removed from the diseased areas by means of bleaching agents like potassium permanganate or sodium sulphite. The normal fibres stain a deep blue-black, and the areas of "demyelination" (where the medullary sheaths are lost) remain quite colourless.

3. *Marchi's* fluid (a mixture of potassium bichromate and osmic acid) does not affect normal nerve fibres, but stains fibres in the early stages of degeneration black. The chromic acid penetrates normal fibres and rapidly oxidizes the unsaturated fatty acids in lecithine, which are then unable to reduce osmic acid. In the degenerated fibre, the fatty acids are in the free state or in some altered form, so that even after treatment with chromic acid, they can still reduce the osmic acid to the lower black osmic oxide.

Function of Nerve Fibres.—Nerve fibre is a tissue in which some of the properties of living matter have become developed to an exceptional extent, especially *conductivity* and *excitability*. In the case of the great sciatic nerve of the frog, the rate of propagation of the nervous impulse is about 28

metres per second ; in man, owing to the higher temperature of the body, the rate of conduction is three or four times as fast—about 120 metres per second. It should be remembered, too, that if any point on the length of a nerve is stimulated, the impulse travels equally well in *both* directions.

Nerve fibres are excitable, the electrical stimulus being the common one employed experimentally, but chemical or mechanical stimuli are also effective. The measure of the excitability of a nerve fibre, at any time and under varying conditions, is the strength of stimulus which must be applied to initiate the nervous impulse. We find that this excitability varies from moment to moment, and with the state of the environment of the fibre, but a certain minimal or *threshold* stimulus is always necessary before the fibre will respond at all. The fibre in the region stimulated becomes " negative " (see p. 230) to the other points on the nerve, and this " *wave of negativity* " spreads out in both directions along the nerve with a velocity equal to that of the nervous impulse ; the electrical change is probably an index of the intensity of the impulse.

Under normal conditions the nervous impulse is conducted along the whole length of the fibre with *undiminished* intensity. If the nerve fibre is poisoned with a narcotic drug like alcohol, the nervous impulse is diminished in intensity in the poisoned area or may be extinguished altogether.

Changes in Nerve after the Passage of the Impulse.—These must be considered in detail, for almost indentical changes occur in heart muscle after the period of activity is over (cf. p. 240). As the subject is a little confusing, we will make clear the terms used :

Exciting " stimulus " is the external force applied to the fibre (electrical, chemical, mechanical, etc.).
Nervous " impulse " : the change of state produced in a nerve when conduction is occurring.
Excitability is measured by the strength of stimulus necessary to initiate the impulse.
Conductivity : ability of the fibre to transmit an impulse.
Intensity of impulse : probably proportioned to the extent of the current of action.

Changes in excitability and conductivity occur after the passage of the nervous impulse, and these changes run parallel to one another. The details to be quoted apply to the sciatic nerve of the frog, and probably analogous phenomena occur in mammalian nerve (Fig. 4).[1] For a period up to 0·003 second following the passage of the impulse the fibre is *absolutely refractory*. No stimulus is sufficiently strong to initiate a fresh impulse, and no impulse can pass through this region. Neither excitability nor conductivity, therefore, is present. The next 0·010 second is a period of *partial refractoriness*. First, a very strong current can excite the fibre, which responds with an impulse of feeble intensity. Gradually the strength of the minimal exciting stimulus falls and the intensity of the impulse rises, until a normal state of affairs returns at 0·013 second. The next stage is a *supranormal* state of functional activity which ends from 0·03 to 0·1 second after the initial impulse passed through the fibre. A stimulus weaker than the normal threshold is

[1] The figures quoted in the text represent average results and differ slightly from those shown in Fig. 4.

adequate to initiate the impulse, and the intensity of the impulse is greater than normal. The supranormal phase is only seen when the nerve is bathed in fluid on the *acid* side of neutrality. We now see why a nerve fibre can respond to continuous stimulation for hours without showing signs of fatigue. The explanation is that the fibre is conducting not continuously but intermittently. Any stimuli falling during the refractory period are ineffective, and the fibre only begins to respond again when it has recovered.

Gasser, Erlanger, and Bishop, using an inertialess system of recording the action current (by means of the cathode-ray oscillograph [1]) have shown that in the case of many nerves it is composed of several superimposed waves. Further analysis has shown that a mixed nerve like the sciatic of the frog contains *four* kinds of fibres (α, β, γ, δ),

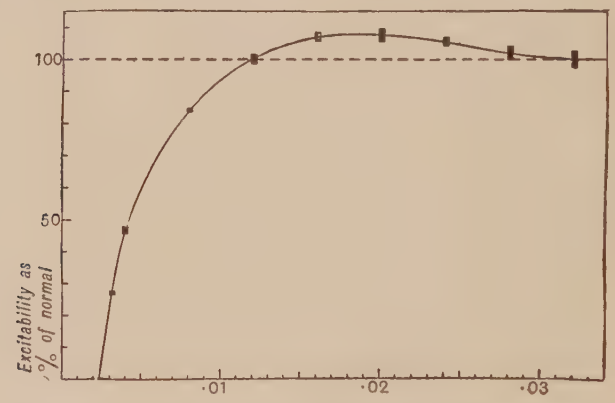

Fig. 4.—Recovery of excitability in sciatic-gastrocnemius preparation of frog. Ordinate = excitability measured in percentages of the normal excitability of resting nerve. Abscissa = time interval between the first and second stimuli. (Keith Lucas, *Conduction of Nervous Impulse.*)

which vary in their properties. The α fibres have the *largest cross-section*, the *greatest velocity* of the nervous impulse, the *lowest threshold* to stimulation, and the *shortest absolute and relative refractory periods*. The β, γ, and δ fibres have a progressively smaller diameter, lower velocity, higher threshold, and longer refractory periods. Thus the velocity of the impulses in the sciatic of the frog are (in metres per second) 47·3, 28·7, 19·0, and 13·6 for the α, β, γ, and δ fibres respectively; again, the absolute refractory periods are α 1·20 σ, β 1·68 σ, γ 3·13 σ ($\sigma = 0{\cdot}001$ second). It has been found that the velocity of the impulse is proportional to the diameter of the fibres. The posterior nerve roots contain all four kinds of fibre, but the α fibres alone are present in the anterior roots. The phrenic nerve also contains α fibres only; it is likely therefore that the α fibres in the posterior roots convey impulses from the deep structures.

[1] *Amer. Journ. Physiol.*, 1922, vol. lxii. p. 496; 1924, vol. lxx. p. 624; 1925, vol. lxxiii. p. 613.

An attempt must be made to describe the nature of the nervous impulse. The working hypothesis is Bernstein's "membrane theory," which will be given in general terms. The fibre is regarded as possessed of a surface layer in a state of unstable equilibrium. In active regions of the fibre, a sudden increase in the permeability of this surface layer occurs, and ions which have been stored up under pressure leak out. This movement of the ions in one section sets up a similar disturbance of ions in adjacent segments. Once the impulse is initiated, it is propagated by changes generated by the fibre itself. When the original equilibrium is restored by the migration back of the ions, the fibre regains its normal properties.

Probably chemical changes occur in nerve during the passage of the impulse. According to Hill, $1{\cdot}0 \times 10^{-7}$ calories are liberated per impulse per gram of nerve. During the recovery period which follows the passage of the impulse more heat is given off ("delayed" heat), which is about ten times as great as the first or "initial" heat (cf. muscle, p. 357); about as much heat is liberated in nerve by the passage of half a million impulses as in muscle by a single twitch. Measurable amounts of CO_2 are given off by nerve during activity, but the figures obtained are too high to be accounted for by the heat liberated. In the absence of oxygen, conduction ceases after some hours.

"All-or-None" Law.—The intensity of the impulse in any fibre is probably quite independent of the strength of the exciting stimulus, providing the latter is adequate. Electrical stimuli below threshold strength elicit no response; if they are of threshold strength or over a nervous impulse of maximum intensity is set up. Either the fibre does not respond at all, or else it responds to the utmost of its ability (under the conditions at the moment). A simple analogy may be given: a certain force must be applied to a trigger before anything happens; but beyond this, the force can be increased indefinitely without causing the bullet to travel any faster. The "all or none" law thus defined applies in all probability to skeletal and cardiac muscle too (see p. 240).

The above argument deals with the response of a single *fibre*. If a nerve *trunk* is stimulated, when the exciting stimulus is increased above threshold a larger number of *fibres* are stimulated. Finally a strength of stimulus is reached which excites all the nerve fibres; increasing the exciting stimulus further gives no greater response from the whole nerve.

Behaviour of Narcotized Nerve.—If nerve fibres are exposed to the action of alcohol vapour or other narcotic substances it is found that the excitability is diminished, conduction is slowed down, and the intensity of the nervous impulse is reduced. It was believed (Adrian, Lucas) that the intensity of the impulse steadily dwindled as it passed through the narcotized region, and if this was of sufficient length, the impulse was finally extinguished altogether. This type of conduction was referred to as *conduction with decrement*. This question has been carefully studied by Kato in Japan and Forbes and co-workers in America.[1] The most important experiment carried out by the latter investigators was as follows: A length of nerve is mounted in a special chamber consisting of several compartments as illustrated in the diagram. A, B are stimulating electrodes; 1, 2, 3, 4, 5, 6 are electrodes 15 mm. apart which lead to a string galvanometer which measures the size

[1] Davis, Forbes, Brunswick, and Hopkins, *Amer. Journ. Physiol.*, 1926, vol. lxxvi p. 448. Kato, *Decrementless Conduction* (Tokyo, 1924).

of the current of action in the corresponding points on the nerve. Pure moist air is circulated through the outer chambers containing A, B, and 5, 6 ; the chamber containing 4 receives no ventilation. Alcohol vapour (or pure air) may be passed through inner chamber containing 1, 2, 3. Electrodes 1 and 3 are 7 mm. from the walls of the chamber (see Fig. 5). Chamber 4 checks leakage from the narcotizing chamber to the control chamber 5, 6. As the alcohol vapour is rapidly bubbled through chamber 1, 2, 3 it probably produces a uniform distribution of narcotic in this part of the nerve. The nerve is stimulated by supramaximal shocks (to ensure that all the fibres are excited) at A, B, and the electrical responses of the varying points along the nerve are measured, first during a control period and then during the period of narcosis, and finally during the recovery process (when the alcohol vapour is displaced by fresh air). It is assumed that the electrical

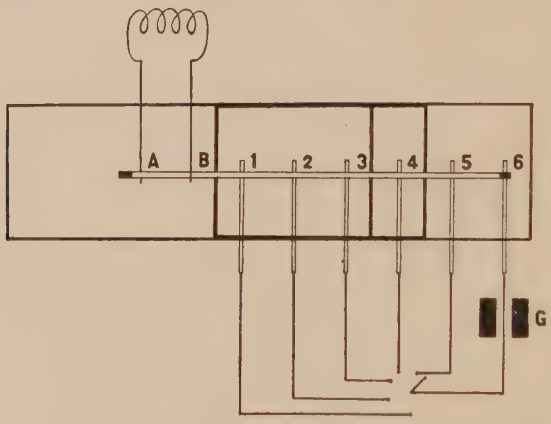

Fig. 5.—Diagram of Chamber and its Connections. (See text.) (Davis, Forbes, Brunswick, and Hopkins, *Amer. Journ. Physiol.*

On nerve, black indicates crushed areas.

response at any point on the nerve is proportional to the intensity of the nervous impulse. The results are illustrated in Fig. 6. The response from lead 6 was unaffected until just before the end ; there was a steady increase of narcosis in the chamber until the intensity of the response fell to 65 to 70 per cent. of the normal ; lead 4 fell off a little, probably owing to slight leakage of narcotic. The important points, however, are : (1) At any given moment the extent of the depression is approximately the same in all three leads in the narcotising chamber. If conduction occurred with decrement, then the intensity at lead 3 should be appreciably lower than at 1, but this is certainly not the case ; the functional capacity of narcotized zone is *uniformly depressed.*[1] (2) The intensity of the impulse in the control

[1] This experiment gives no information about the behaviour of the nervous impulse in the *first* 7 *mm.* of the narcotized zone *i.e.* between the wall of the chamber and lead 1. Kato believes the intensity of the impulse diminishes suddenly as soon as it enters the narcotized area ; Forbes thinks it may fall off gradually (*i.e.* conduction with decrement *may* possibly occur for a few millimetres), but as far as the rest of the length of the narcotized nerve is concerned, the intensity is proved to be *uniformly* depressed.

region 5 is normal. Once the impulse leaves the narcotized area and reaches normal tissue, the intensity rises once more to its original level. The intensity of the impulse at any point on the nerve depends entirely on the local conditions. The exciting stimulus produces the initial change in a certain region of the fibre ; the presence of this " change " in one spot produces a similar " change " in adjacent spots, and so the wave of " change " travels along. Healthy nerve reacts vigorously when this change reaches it ; narcotized nerve responds poorly, *i.e.* the intensity of the impulse locally is feeble ; if the change can get through the narcotized zone and reach healthy nerve again, the original intensity of the impulse is restored. When the intensity of the response of the narcotized portion of the nerve falls to 70 per cent. of the normal, it is likely that some of its fibres (probably the

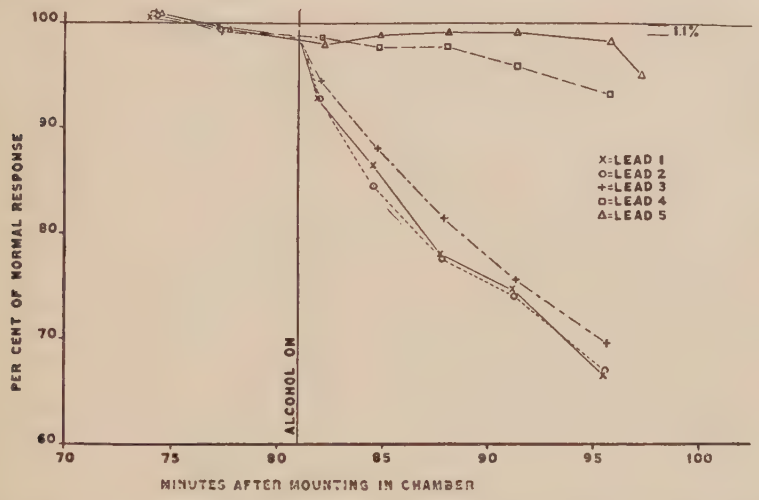

Fig. 6.—Effect of alcohol vapour on electrical response of excised peroneal nerve of cat. Leads 1, 2, 3 are from narcotized region (cf. Fig. 5). Note parallel course of depression of response at these points. Leads 4 and 5 are controls. (Davis, Forbes, Brunswick, and Hopkins, *Amer. Journ. Physiol.*)

more external ones) cease to conduct altogether ; for it is now found that the response from control lead 5 falls appreciably (see Fig. 6). As the impulse was completely extinguished in some of the fibres in the narcotized area, fewer fibres were excited in the control region 5, and so the total response there is diminished. If the response in the narcotized region falls to 20 per cent. of normal, 50 per cent. of the fibres are completely blocked, for the response in the control zone 5 is diminished to this extent. When the alcohol vapour is replaced by pure air, the portions of the nerve under leads 1, 2, 3 recover equally rapidly.

Reflex Action.—Certain general aspects of reflex action will now be considered.

1. Localization.—To elicit any reflex, the stimulus must be applied to a particular region of the body. To produce the flexor reflex, *q.v.*, the sole of the

foot, or some part of the lower limb, must be stimulated. The basis of localization is primarily anatomical. As the afferent impulse enters the cord it connects up most readily with certain motor neurones, to which the impulse tends to spread.

2. Irradiation.—As the strength of the initial stimulus is increased, the impulse tends to spread up and down the cord and involve a greater number of efferent neurones. Thus weak stimulation of the sole of the foot produces a movement of the toes only. More powerful stimuli may elicit flexion of the whole of the lower limb.

3. Delay.—Every reflex action takes time. Part of this time is taken up in the passage of the impulse in the peripheral nerves, and in the latent period of the receptor organ (sensory nerve ending) and the effector organ (the muscle). If this is deducted from the "total reflex time," the "reduced reflex time" is obtained, which is spent in traversing the central nervous system. The delay is believed to occur at the "synapse," where conduction is slower than in nerve fibre, or at the membrane of the nerve cell, where chemical or physico-chemical changes are probably set up (p. 19). In the frog the delay at a synapse may be 0·002 to 0·003 second.

4. Fatigue of reflex activity occurs rapidly, and first develops at the "synapse." When the flexor reflex, for example, can no longer be elicited, the movement can still be produced by directly stimulating the motor nerves. In other words, the peripheral nerves, the nerve endings, and the muscle are still unaffected.

5. Block or Resistance.—An impulse cannot pass backwards through a synapse, *i.e.* it can pass from the terminations of the axon to the dendrites of the adjacent neurone, but not in the reverse direction. In this connection the peripheral fibres of the posterior root ganglia and their sensory cranial homologues must be regarded as equivalent to dendrites, while the central fibre is the true axon. The term "*law of forward conduction*" is applied to this fixity of direction of impulse-conduction in the nervous system.

6. Summation.—If a too feeble or subminimal stimulus is applied to the sole of the foot, it proves ineffective at first. But if the stimulus is repeated at a definite rate, the reflex is finally elicited, even when a stronger single stimulus fails to achieve any result (see p. 20).

7. Inhibition.—Two types of inhibition may be recognized—inhibition of reflexes, and inhibition of muscles. It is obvious that as so many afferent impulses are constantly clamouring for access to the afferent mechanisms, some arrangement must be present to enable one reflex to prevail and to prevent other reflexes from interfering with it and nullifying its effectiveness. We consequently find, if stimuli are applied simultaneously, calculated to produce antagonistic effects, the resultant is not the algebraic sum of the responses, but one reaction alone may prevail; *e.g.* if the sole of the foot is stimulated with a nocuous stimulus to elicit the flexor reflex and at the same time pressure is applied to produce the "extensor thrust," it is found that the flexor reflex alone will result. The extensor thrust is prevented or only comes on after long delay. "Every effective reaction inhibits every other reaction that would employ the same common path" (Sherrington).

8. "After discharge," "Recruitment," and "Rebound" (see p. 20).

Sherrington's "Humoral" Theory of Excitation and Inhibition.—It is assumed that when an impulse along an afferent nerve ends in the central nervous system it causes to be liberated a quantum of a chemical

substance which becomes dissipated spontaneously, but more slowly than the dying out of the nervous impulse, which is of extremely brief duration. The process of liberation of this chemical body possesses no refractory phase, so that it may accumulate if nervous impulses arrive in rapid sequence at the central organ. The substance liberated may be excitory (E substance or E) or inhibitory (I substance or I). It is assumed that E, for example, is multiplied twofold in amount by two impulses following in rapid sequence, being diminished only by the relatively slight dissipation of E in the interval between the impulses. The afferent fibres are regarded therefore as secretory nerves ; E and I may consist of physico-chemical changes rather than be chemical bodies, but it is assumed that I has the power of neutralizing the effect of E as acids neutralize alkalis. Cajal has shown that afferent fibres end in small knobs—"pieds terminaux"—on the membrane enclosing the anterior horn cells ; these may conceivably be the locus of liberation of E and I, and possibly these terminals are of two kinds, some liberating E and others I. It must further be recalled that one afferent nerve ends round several anterior cells, and that each anterior cell receives collaterals from *several* afferents. The term motor units, which will be employed in the discussion following, refers to the anterior horn cell (motoneurone), its axon, and the corresponding muscle fibres.

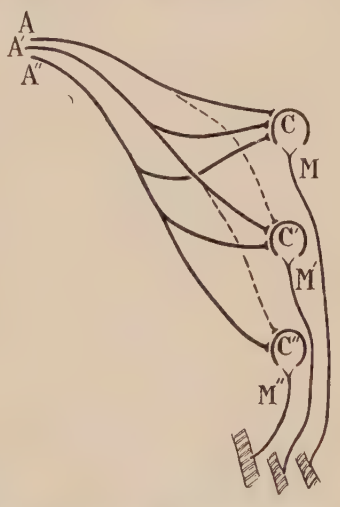

FIG. 7.—Diagram to illustrate Humoral Theory of Reflex Action. (Sherrington, *Proc. Roy. Soc.*, 1925.)

Sherrington's diagram (Fig. 7) may make the position clearer. A, A′, and A″ are afferent fibres which produce pure excitation of the muscle fibres M, M′ M″ through the intermediary of units in the central nervous system C, C′, C″. A has the lowest threshold to stimulation, A′ a higher, A″ the highest threshold. The thick lines from A, A′, and A″ represent main terminals, the dotted lines subsidiary terminals. Thus A has a main terminal at C and subterminals at C′, C″. The main terminals are supposed to liberate individually an amount of excitory substance of value 1, which quantity is supposed to be just adequate to stimulate the motor units. The subterminals are supposed to liberate subliminal values of E, *e.g.* 0·5.

The following facts of reflex action can be readily understood on the basis of the schema :

1. Increase in the *intensity* of a single shock stimulus applied to an afferent nerve causes increase in the muscular response : if the stimulus is of an intensity to stimulate A only, E of value 1 is liberated at C by the main terminal, and E 0·5 by the subterminals at C′, C″ ; M therefore contracts, M′ and M″ do not. If the stimulus is of an intensity to stimulate A and A′ but not A″, E of value 2 is liberated at C (from main terminals of A and A′), E 1·5 at C′ (from main terminal of A′ and subterminal

of A), and E 0·5 at C″ (from subterminal of A′). M and M′ contract, but M″ does not.

2. *Summation* produced by repetition of stimuli which individually are ineffective : a single stimulus produces a subliminal amount of E ; repetition causes E to accumulate till it reaches a concentration which is adequate to excite the motoneurones.

3. Increasing the *frequency* of stimulation increases the motor response : each impulse which passes along the nerve results in the liberation of E at each of the terminals ; if the impulses generated per second are numerous, threshold amounts of E will be accumulated at the minor terminals, and thus activate a greater number of motoneurones.

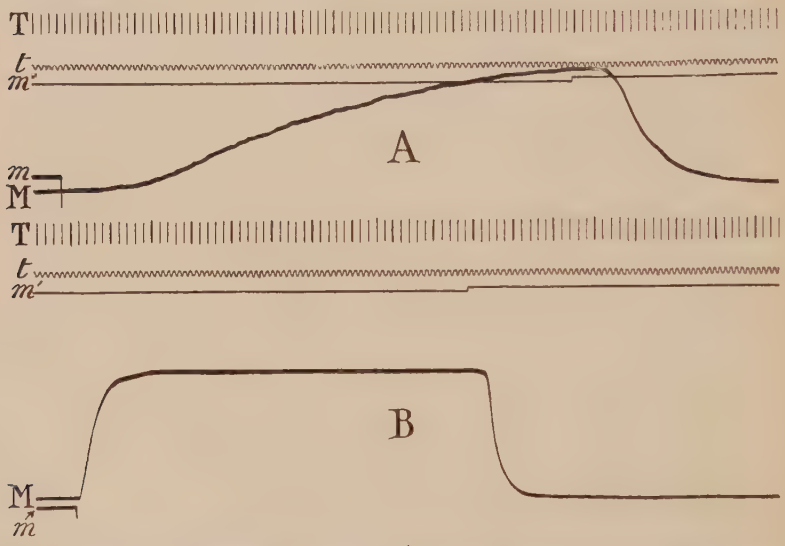

Fig. 8.—The Crossed Extensor Reflex of Quadriceps compared with the Response of that Muscle to stimulation of Motor Nerve. (Liddell and Sherrington, *Proc. Roy. Soc.*, 1923.)

A. Reflex contralateral peroneo-popliteal stimulation coil 14·5 cm., frequency 38 per sec. ; B. Motor nerve stimulation coil 22 cm., frequency 38 per sec. ; T, 0·04 sec. ; *m*, beginning, *m′*, end of stimulation (isometric records).

4. "*Recruitment*" and "*after-discharge*."[1] These features are best studied in the "crossed extensor reflex," which consists of contraction of the quadriceps as a result of stimulation of a sensory nerve in the opposite limb.

If a motor nerve is stimulated with a tetanizing current for a given time, it is found that after a brief latency the tension developed by the muscle rises sharply to a maximum. When the stimulus is discontinued, the tension diminishes rapidly as the muscle relaxes. If the crossed extensor reflex is elicited there is a longer latency, which is characteristic of reflex activity ; under continued (faradic) afferent stimulation the tension in the quadriceps rises relatively *gradually* to its maximum (see Fig. 8).

[1] Liddell and Sherrington, *Proc. Roy. Soc.*, 1925, vol. xcvii. p. 488.

If the muscle fibres are under the same conditions in both experiments and the same tension is developed in both, then, according to the " all or none " law, the same number of muscle fibres are concerned in both reactions. The rapid rise of tension in the motor tetanus means that all the muscle fibres contracted practically synchronously; the slower development of tension in the reflex contraction suggests that first a few muscle units were affected, and gradually more and more became involved until the full quota was in action. In other words, under continued (faradic) excitation of an afferent nerve an increasing number of motor neurones are brought under excitation: this is called " excitory recruitment," and in terms of the diagram (p. 19) means that, as the stimulation is continued, more and more E substance is accumulated at the minor subterminals until the corresponding

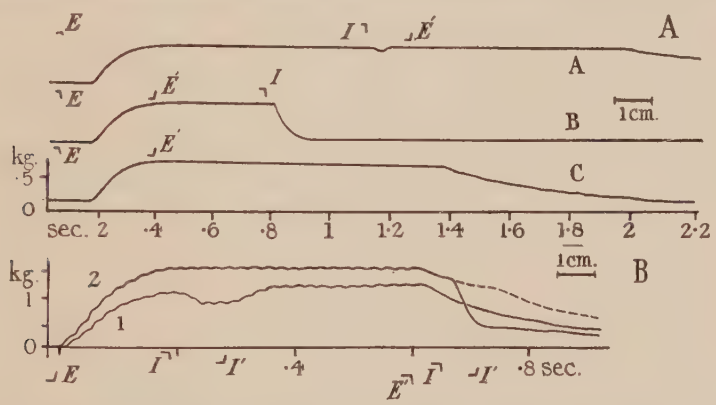

FIG. 9. *A*, Vasto crureus. Inhibitory distinction between " Stimulation Plateau " and " After-discharge Plateau " of Reflex Contraction. E to E', stimulation of afferent nerve to elicit crossed extensor reflex; I, delivery of single break shock to inhibitory afferent, at 12 cm. coil distance; A, delivery of inhibition in " stimulation plateau "; B, delivery of inhibition in " after-discharge plateau "; C, repetition of reflex B with no inhibitory shock delivered. Tendon movement multiplied forty-five times.

B, Semitendinosus, a flexor. The broken line gives the course of the after-contraction in the control (uninhibited) reflex. 1. Inhibitory stimulus (I to I') during stimulation plateau; 2. Inhibitory stimulus in after-discharge. (Liddell and Sherrington, *Proc. Roy. Soc.*, 1925.)

cells receive a dose of E sufficient to arouse them to activity. It is noteworthy that indefinite prolongation of the afferent stimulus does not produce unlimited recruitment: a "*stimulation plateau*" is reached (see Fig. 9); there is a limit to the number of neurones that can be recruited. Afferent nerves are connected with a finite number of motor neurones, and not, as previously imagined, with every motor cell in the body. Although strychnine facilitates E formation (p. 25) and enhances reflex contraction, it, too, does not give rise to unlimited recruitment. On discontinuance of afferent stimulation the tension may remain unaltered for several seconds, long after the nervous impulses set up by the afferent stimulus must have died away. This is called the "*after-discharge plateau*"; as it is equal in height to the stimulation plateau, it means that *all* the motor neurones which were excited in the reflex are still discharging. Afferent stimulation piled up supra-maximal

quantities of E, and until the concentration of E falls below threshold value for any of the neurones the muscle tension remains unaltered. When relaxation of the muscle sets in it is a more gradual process than in the case of the motor tetanus. In the latter all the muscle units go out of action together; in the former the concentration of E falls below threshold first round the more outlying neurones and the corresponding muscle units relax; the dissipation of E gradually proceeds till all the motor neurones come to rest. Recruitment thus gives *inertia* and after-discharge provides *momentum* to reflex movements, making these movements smoother in onset and termination.

By inspection of the curve it is difficult to make any distinction between the stimulation and after-discharge plateau (Fig. 9). A striking difference is readily demonstrated by throwing in a single stimulus of given intensity to an ipsilateral nerve, which tends to cause inhibition of the quadriceps. In the stimulation plateau it only produces a slight temporary notching of the curve: the I formed by the inhibitory afferent neutralized some of the E which had accumulated, a few neurones went temporarily out of action, but were soon activated again. The same dose of I in the after-discharge plateau acts on the E which was left over after excitatory stimulation, *i.e.* at a time when fresh development of E is no longer taking place; it therefore produces a much greater effect, for all the neurones round which E falls below threshold value cease to act and do not become excited again. Extensive and rapid relaxation of the muscle occurs.[1]

Recruitment and after-discharge also characterize *inhibitory* reflexes. These can only be studied against a background of reflex excitation, *e.g.* crossed extensor reflex. These features are well seen in Fig. 10 (see legend).

The Final Common Path.—At the commencement of each reflex arc there is a receptor neurone reserved exclusively for impulses generated at one single receptive source. The motor neurone, however, receives impulses from many receptive sources. "It is the sole path which all impulses, no matter whence they come, must travel, if they are to act on the muscle fibres to which it leads. Reflexes originating at different distant points and passing through paths widely separate in the brain, converge to the same motor mechanism—the *final common path*, and act harmoniously upon it. The motor neurones of the knee muscles, for example, are employed in reflex arcs arising in the same or opposite foot, olfactory organ, and labyrinth" (Sherrington). In our subsequent analysis we shall find many impulses acting *harmoniously* on the final common path, the lower motor neurone.

Reciprocal Innervation of Muscles.—Reflexes are co-ordinated movements in which certain muscles (agonists) shorten to produce movement at a joint. The muscles that would tend to antagonize the movement (antagonists) are simultaneously depressed or inhibited. This important general law may be demonstrated in various ways.

1. In a spinal animal the flexors of the knee and their antagonist the vasto-crureus muscle may be detached from their insertions and attached to levers. If a nocuous stimulus is applied to the sole of the foot to elicit the flexor reflex, it is found that the flexors contract and the extensors elongate. It can be shown that the two processes are simultaneously induced. The

[1] The crossed extensor reflex shows other features of interest when the quadriceps is allowed to shorten freely, *i.e.* when the contraction is isotonic (see p. 55, Fig. 23).

receptive field, the nature of the stimulus, the latent period, the number of subminimal stimuli necessary to produce summation are identical for contraction of the hamstrings and for relaxation of the vasto-crureus. The afferent impulse on entering the spinal cord stimulates one group of anterior horn cells and inhibits the cells supplying the antagonists (Fig. 11).

2. The knee jerk may be taken as an index of the state of tone in the quadriceps muscle. In a decerebrate animal the knee jerk is elicited at

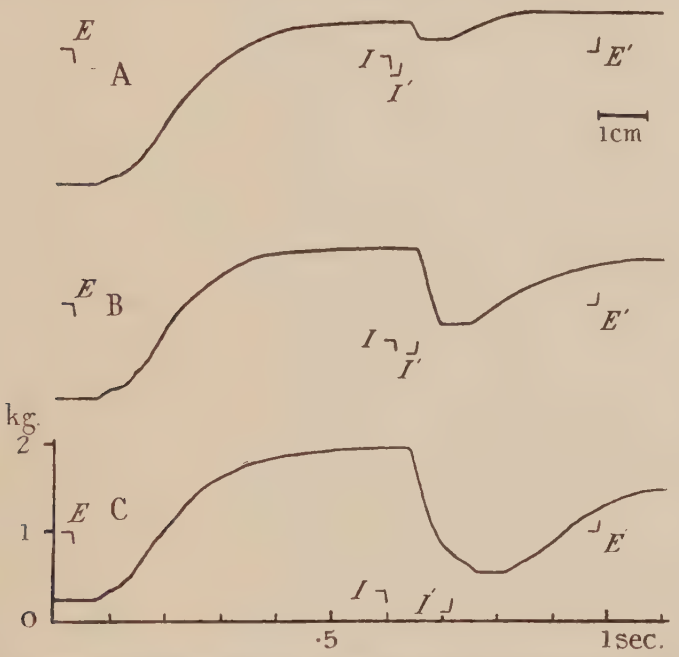

Fig. 10.—"Inhibitory Recruitment" and "After-discharge." Rectus femoris and part of Crureus. E to E′, stimulation of afferent nerve to elicit reflex contraction; I to I′, stimulation of inhibitory afferent by double shocks at 95 p.s. and 16·5 cm. coil distance. Duration of tetanic stimulation of inhibitory afferent longer in B than in A, in C than in B. Tendon movement multiplied fifty times. Time in tenths of seconds. (Liddell and Sherrington, *Proc. Roy. Soc.*, 1925.)

Note that prolongation of inhibitory stimulation increases the extent of the inhibition; following it is horizontal plateau which is interpreted as representing inhibitory after-discharge; the inhibitory state persists in nerve centres and prevents for 0·05 sec. the redevelopment of tension in the muscle.

regular intervals by tapping the patellar tendon, and the responses are recorded. A weak stimulus is applied to the sole of the foot, too feeble to produce a flexor movement, but sufficient to cause the flexor muscles to harden. Inhibition of the quadriceps occurs, and is at once shown by depression or disappearance of the knee jerk. The knee jerk is again normally obtained when the stimulation of the sole is stopped (cf. p. 53).[1]

[1] For other examples see pp. 50, 65, and Fig. 28. Reciprocal innervation can also be demonstrated in voluntary movements (p. 66), and following stimulation of the motor cortex (pp. 70, 73).

Discharge of Nerve Centres.—Because of the intermittent nature of conductivity in nerve, it is clear that the discharges from the nerve centres must be discontinuous too. Every contraction of a skeletal muscle is in the nature of a brief *tetanus*, and results from a series of rapid stimuli sent out from the nerve centres. Each twitch of the normally acting diaphragm results from 80 to 180 impulses sent out at the rate of 70 to 100 per second.

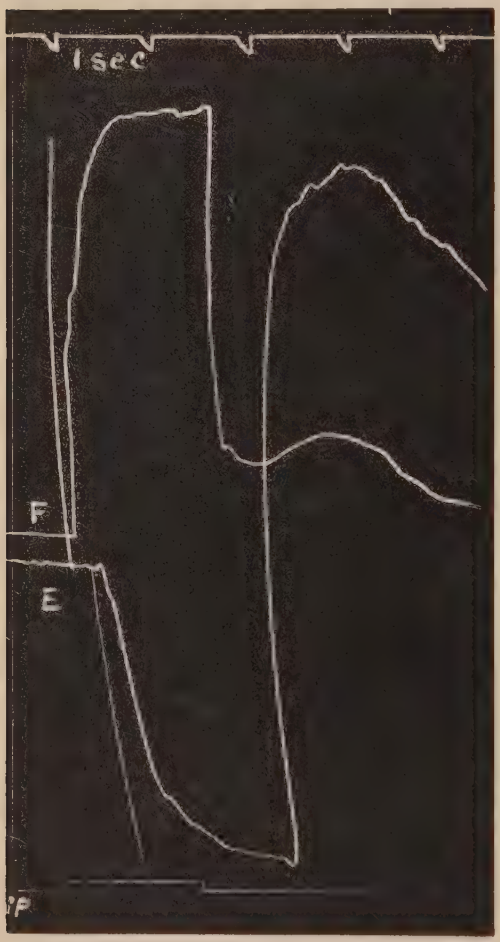

FIG. 11.—Reciprocal Reflex of Antagonistic Muscles of Knee. F, semitendinosus, a knee flexor; E, vasto-crureus, a knee extensor; IP, ipsilateral popliteal nerve. The inhibition of the extensor is followed by a marked *rebound contraction* above original level; this is accompanied by a simultaneous relaxation of the flexor muscle. Decerebrate cat. Myograph writer for E is set a little to the right of that for F, so that ascent of F and descent of E are in fact practically synchronous. (Sherrington, *Quart. Journ. Exp. Physiol.*, 1913.)

Action of Strychnine and Tetanus Toxin.—Strychnine and tetanus toxin produce their effects by heightening the excitability of the central nervous system; with large doses of strychnine, convulsions are provoked as a result of the slightest stimulus applied to the body. The state of functional activity at the "synapses" is heightened, and widespread irradiation takes place up and down the nervous system, and many of the lower motor neurones may be involved. The convulsions, however, are not co-ordinated movements: simultaneous contraction of agonists and antagonists may occur. Characteristically there is tonic contraction of the muscles which produces arching of the back.

Recent work has thrown new light on the mode of action of strychnine. It was previously believed that strychnine reverses the central processes of inhibition and converts them into excitation. The experiment which was thought to demonstrate this was as follows: In the dog, cut the nerves to

all the muscles acting on the knee-joint, with the exception of the nerve to the vastus crureus. Isolate the internal saphenous nerve just below the knee. Stimulation of the central end of this nerve normally produces inhibition of the quadriceps. When increasing doses of strychnine are injected (but not enough to induce convulsions) the inhibition obtained becomes less marked, and is finally replaced by contraction of the quadriceps.

It is found, however, that certain inhibitory responses are *not* reversed by strychnine, *e.g.*: (1) Inhibition of decerebrate rigidity from stimulation of the palæovermis (p. 87); (2) inhibition of the stretch reflex on pulling the antagonistic flexors (p. 53). The latter particularly is a more "natural" way of producing inhibition than by stimulating a bared afferent nerve, and it is likely that in that experiment *homogeneous* inhibitory impulses are set up. Any afferent nerve probably contains a mixture of inhibitory and excitory fibres; in the case of the saphenous nerve, inhibitory fibres to the quadriceps predominate. Strychnine probably *facilitates the process of excitation* (possibly it stimulates E formation), so that the excitation set up by the central end of the nerve instead of being relatively unimportant entirely overcomes the concomitant inhibitory process.

Movements initiated from the cortex are also affected by strychnine. Normally the movements of opening the jaw or flexion of the elbow can be elicited from a large part of the face and arm area of the cortex respectively. The opposite movements are rarely obtained. After small doses of strychnine, the very area which gave opening of the jaw now produces closure of the jaw; extension instead of flexion of the elbow is likewise obtained. If tetanus toxin is injected into the motor nerves of one limb, it is known to ascend along the nerve trunks to reach the grey matter of the spinal cord. Abnormal movement from cortical stimulation will then occur first in that limb. These results are difficult to interpret: it seems as though one must say that the impulses passing down from the stimulated motor cortex are not homogeneous either.

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THE AFFERENT NERVOUS SYSTEM

Peripheral nerves — Nerve endings — Temperature — Touch — Action currents in sensory nerves—Properties of sense organs—Dilator fibres in posterior nerve roots—Sensory conduction in the spinal cord—Syringomyelia, etc.—Tabes—Conduction in the brain stem—Optic thalamus—Thalamic syndrome—Sensory cortex—The auditory path—Tests for deafness—Visual path—Visual reflexes—Argyll Robertson pupil—Taste path.

The study of the afferent nervous system presents considerable difficulties: firstly, because we are dependent almost entirely upon observations on the human subject, especially of patients afflicted with injuries to various parts

of the nervous system. We obtain little assistance from animal experimentation because such investigations are obviously very difficult to carry out, and one would naturally expect the greatest divergence between the highly organized nervous system of man and that of the lower animals. Then we shall find that sensory impulses on their way from the periphery to the cortex are undergoing rearrangement at different levels, notably, on entering the spinal cord and on reaching the thalamus. We have to discuss the mode of conduction of the sensory impulses, and their special characters in the peripheral nerves, the spinal cord, the brain stem, the thalamus, and the sensory cortex.

In the Peripheral Nerves.—The sensory impulses in the peripheral nerves are carried, partly, in (so-called) *motor* nerves and partly in cutaneous *sensory* nerves.

(*a*) The former convey impulses from the deep structures, such as the muscles, tendons, ligaments, periosteum, and joints, and it is obviously a very convenient arrangement, anatomically, that the nerve supplying a muscle with motor fibres should also convey the sensory impressions back to the spinal cord. The term " motor nerve " to a muscle is, strictly, a misnomer, because it is really a mixed motor and sensory nerve. Sherrington has shown that about 40 per cent. of the fibres in a " motor " nerve are afferent, and have their cells of origin in the posterior root ganglion. The term " muscle " nerve would perhaps more accurately describe the function of the nerve.

(*b*) In contrast with these impulses of " *deep sensibility*," as they are called, carried by the motor nerves, we have those of *superficial* sensibility, conveyed by the cutaneous sensory nerves from the end organs in the skin. We can further subdivide these into (i) a *protopathic* group of crude and primitive sensations, and (ii) an *epicritic* group of more highly differentiated sensations. This subdivision may possibly have an evolutionary origin—the crude protopathic sensibility being the earlier to appear, while epicritic sensibility may only have developed later in the history of man.

We may summarize these statements thus :

Sensation in Peripheral Nerves—

1. Superficial { (*a*) Epicritic. (*b*) Protopathic.
2. Deep.

This subdivision depends on the classical experiments of Head and his co-workers. The radial and external cutaneous nerves were exposed in the neighbourhood of the elbow. Small portions of these nerves were cut out, and the ends were then united with silk sutures. All forms of cutaneous, *i.e.* superficial, sensibility were at once abolished over the radial half of the forearm and the back of the hand. The softness of cotton wool, the prick of a pin, and the application of heat, were not appreciated. A certain degree of sensibility, however, was retained, and that must have been mediated by afferent fibres running in the motor nerves. This *deep sensibility* enables pressure to be appreciated ; any stimulus producing deformation of structure is recognized. Excessive pressure gives rise to aching pain. Awareness of the position of the part, and of movements passively imposed upon it, are also retained.

Protopathic sensibility begins to return after seven weeks and is complete in about thirty weeks. It is a "punctate" form of sensibility, and depends on the regeneration of the nerve supply to certain specially sensitive *pain* spots, *heat* spots, and *cold* spots. The intervening areas of skin remain insensitive. It is claimed that the time taken for the recovery of protopathic sensibility is independent of the length of fibre to be regenerated.

Pain.—A pin-prick cannot be located accurately, and the pain radiates widely and is not infrequently referred to some part at a distance from the point actually stimulated. A stronger pain stimulus than normal is necessary before it can be appreciated—in other words, the threshold for pain is high. The reaction excited is excessive and "sickly" in character; the stimulus gives rise to greater pain on the affected side than does a like stimulus on the normal side.

Temperature.—A sensation of cold is produced by temperatures below 24° C. Similarly, a sensation of heat results from temperatures above that of the body—the lower limit being between 38° to 45° C. It is impossible to recognize any temperature quality between 24° and 38° C. Thus extremes of temperature are recognized as "cold" or "hot" respectively, while intermediate grades give rise to no sensation of temperature whatever. The arrangement may be compared with a greenhouse with a maximum and minimum thermometer connected up in such a fashion that if the temperature exceeded 38° a bell would ring, and if it fell below 24° a siren would blow. We would know if the temperature exceeded 38° or fell below 24°, but not to what extent it did so, and if the temperature was between 24° and 38° we would receive no information at all.

With the return of protopathic sensibility the trophic changes in the skin, which may result from unappreciated cuts and burns, begin to heal rapidly. Normal growth of the part is also restored. It has been claimed that protopathic sensibility is conveyed by non-medullated fibres. As the impulses from any point pass along these uninsulated nerve fibres there may be a tendency for the stimulus to spread over to adjacent fibres; the result is that the impulse appears to come from a much more widespread area than is actually the case.

Epicritic sensibility returns later than protopathic, the exact time depending on the length of the nerve involved. Complete recovery in the case of a long nerve may be delayed for two years or more. Intermediate grades of *temperature* can now be recognized. *Tactile localization*—the ability to recognize the exact spot touched—is restored. *Tactile discrimination* returns; two compass-points held close together are recognized as two distinct points. Light touch, *e.g.* with cotton wool, is now appreciated. Abnormal radiation ceases, and the quality of the sensation becomes normal in character.[1]

We may now describe briefly the structure of the more important sensory nerve endings. They may be classified as follows:

1. Muscle spindle: in muscle.
2. Organ of Golgi: in tendon.

("Muscle sense" or kinæsthetic sensations.)

[1] Sharpey-Schafer (*Quart. Journ. Exp. Physiol.*, 1928, vol. xix. p. 85) has repeated Head's experiments. He finds that after *crushing* a sensory nerve recovery of sensation takes place much more rapidly than after section. Head's results have also been criticized by Trotter and Davies.

3. Special cutaneous sense organs—
   (*a*) Pacinian corpuscle.
   (*b*) Tactile corpuscle. (? Touch.)
   (*c*) End bulbs. (? Temperature.)
4. Free terminal ramifications. (Pain.)

1. Muscle Spindle.—This is a fusiform body lying between the muscle bundles, with its long axis parallel to them. It is 1 to 4 mm. long, and about 0·1 to 0·2 mm. in diameter. It consists of a connective-tissue sheath within which are a number of undifferentiated muscle fibres—"intrafusal fibres."

Large nerve fibres pass to the spindle, break up into branches, and lose their medullary sheaths. The axis cylinders divide, and wind in a spiral manner round the intrafusal fibres. Presumably, changes in the tension of the muscle serve as a stimulus to the spindle; afferent impulses then pass along the motor nerves as described to the posterior nerve roots, their cell station being in the posterior root ganglion.

2. Organ of Golgi.—These endings are found in tendon close to the point of attachment to the muscle. The end of a muscle is enclosed by the sarcolemma, to the outside of which the tendon is joined. The tendon fibres separate into a number of small bundles; nerve fibres penetrate between the fasciculi, and their medullary sheaths stop short; the axons end in terminal arborizations beset with irregular varicosities.

3. Cutaneous Sense Organs.—The special cutaneous sense organs are built on a uniform plan. They consist of an outer lamellated connective-tissue capsule, and a core of soft material—chiefly nucleated protoplasmic cells. Within this core the axon ends simply, or by means of an arborescence. The different organs to be described vary chiefly in the complexity of their design.

(*a*) *Pacinian corpuscles* are found in the subcutaneous tissues of the hands and feet. The capsule consists of a number of concentric fibrous coats arranged like the layers of an onion. The soft core is cylindrical in shape. The nerve fibre loses its sheath and passes down the middle of the core to its further end to form a terminal arborization.

(*b*) *Tactile corpuscles* are found in the papillæ of the skin. They are ellipsoidal in shape. The nerve fibre winds once or twice round the corpuscle to reach its distal part. It then enters, loses its medullary sheath, and ends in a complex ramification.

(*c*) *End bulbs* occur in the conjunctiva, the papillæ of the lips and tongue, the sheaths of nerve trunks, the skin of the genital organs in both sexes, and in the neighbourhood of joints. They are spherical in shape, but otherwise resemble the tactile corpuscles.

4. Free Nerve Terminations are found in the cornea, larynx, and other epithelia. The nerve fibres form a plexus under the epithelium from which fibres proceed to ramify between the epithelial cells.

A few words on terminology may be helpful. Afferent impulses may be divided into—

i. "*Extero-ceptive*": those coming from the outer world, such as impulses of touch, pain, or temperature.

ii. "*Proprio-ceptive*": coming from the muscles and adjacent deep structures, *e.g.* ligaments, tendons, joints, and from the labyrinth. The

impulses from the muscles, tendons, etc., are often referred to as "kinæsthetic" impulses. Proprio-ceptive impulses give information about the position of the head and the various parts of the body at rest and during movement.

iii. "*Entero-ceptive*": arising from the internal organs and viscera.

A few details will follow concerning the nature of cutaneous sensations.

Temperature.—The end organs in the skin are not definitely determined, but are believed to be the end bulbs. A body which has the same temperature as the skin will produce no sensation of temperature. If a suitable instrument be warmed, and passed over the skin, it will be found that at certain points vivid appreciation of warmth occurs: these are the "warm" or "hot" spots. Similarly, "cold" spots may be mapped out. The two types of spot do not coincide with each other, and their distribution in different subjects varies considerably. They cannot be stimulated with the interrupted current if thermal stimuli are avoided, nor do they respond to mechanical irritation. The "cold" spots are about four times as numerous as the "warm" spots. They are found most on the chest, nipples, nose, anterior surface of the arm and forearm, and on the abdomen. They are less numerous in exposed parts such as the face, hands, and mucous membranes.

The spots themselves give a much more intense sensation than the normal skin; localization of the stimulus is imperfect, and there is no power of adaptation.[1] They do not respond to temperatures between 26° and 37° C. The "warm" spots are not stimulated by cold. Temperatures over 50° C. elicit a feeling of tingling giving rise to pain. Temperatures above 44° C. applied to the cold spots give a keen sensation of cold—"paradox" cold. The above observations are best made when protopathic sensation is alone present, because the skin between the sensitive spots is then quite anæsthetic.

Intact skin, in which epicritic sensibility is present too, behaves quite differently. It responds less intensely and can react to intermediate grades of temperature, *i.e.* between 25° to 37° C. It is also capable of adaptation.[1] This power of adaptation is well shown by the three basins experiment. One hand is plunged into hot water and the other into cold water for a few moments. They are then both placed into a basin of tepid water. One hand has a sensation of warmth, the other of cold. If all the "hot" and "cold" spots are marked out, the areas of skin between them are found to be insensitive to *punctate* thermal stimuli, but they respond to *extensive* stimuli. There thus appears to be a double thermal mechanism: the "spots" for intense appreciation of extremes of temperature, and some unknown nerve endings for the recognition of intermediate grades of temperature.

The acuteness of the temperature sense depends on the condition of the subject. It is diminished by fatigue or if the skin is very hot or cold.

Touch.—The end organs of touch are probably the tactile corpuscles. This sensation is investigated by means of Frey's hairs. These hairs are made of varying cross-section, and when bent they exert a varying pressure, which depends on their thickness.

Many touch spots are found round the hair follicles. A slight touch to the hair acts in the same way as a stimulus applied to the long arm of a

[1] Cf. p. 32. Intact skin shows adaptation to temperature, but "hot" and "cold" spots do not.

lever—the short arm of the lever being the root of the hair which is inside the skin. The stimulus is thus multiplied about fivefold during transmission through the hair. Consequently shaving the skin considerably diminishes its sensibility.

Touch spots are most numerous on the finger-tips, and very sparse on the shoulders and the shins. The most sensitive areas of the body are the tongue, nose, lips, and finger-tips. When a stimulus is continued for some time it becomes ineffective—*e.g.* the continual stimulus of clothing is not appreciated because adaptation rapidly takes place (see p. 33).

The touch spots have no relation to the temperature spots. The adequate stimulus for touch spots is provided by deformation of the skin by pulling or pushing. Uniform pressure is ineffective.

Action Currents in Sensory Nerves (Adrian).[1]—With a four-valve

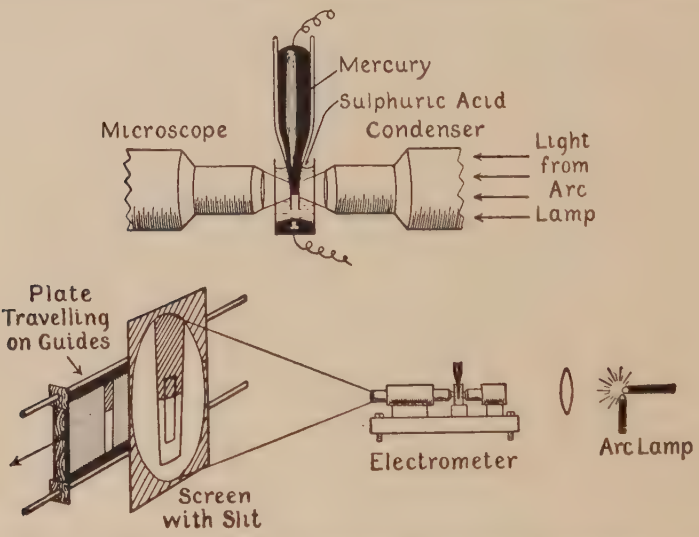

Fig. 12. Diagram of Capillary Electrometer and Photographic Apparatus. (Adrian.)

amplifier it is possible to multiply the potential difference of the action current about 1800 fold; it is then sufficiently large to be recorded by means of a capillary electrometer.[2]

[1] Adrian, *Journ. Physiol.*, 1926, vol. lxi. p. 49; Adrian and Zotterman, *ibid.* pp. 151, 465. Figs. 12, 13, 14, and 15 are reproduced from Adrian's *Basis of Sensation* (London, 1928) by permission of the author and the publishers (Messrs. Christophers).

[2] This consists of a column of mercury in a vertical glass tube which dips into sulphuric acid. The lower part of the tube is drawn out into a fine conical capillary with an open end. The mercury comes to rest in the capillary at a point where a balance is struck between the two opposing forces which are operating, *i.e.* (i) gravity and air pressure which force the mercury down, (ii) surface tension of the face of mercury which tends to push it up the tube. If a difference of electric potential is set up between the mercury and the acid, the surface forces change and the mercury meniscus moves up or down the tube to a new position of equilibrium. This movement is recorded by throwing a beam of light on the tube to cast a shadow of the mercury column on a slit placed in front of a moving photographic plate.

This apparatus can record faithfully such changes of potential as a few millionths of a volt, even when they occur with a frequency of several thousands per second. It thus becomes possible to record the action current in a *single* afferent fibre.

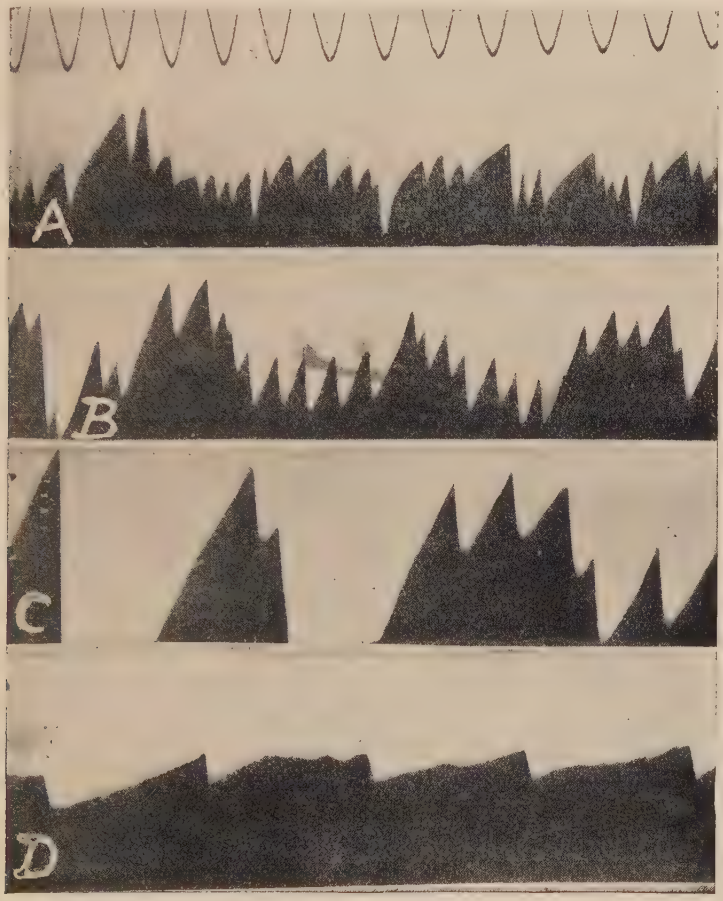

Fig. 13.—Afferent Impulses from Nerve when Muscle is stretched by a weight applied 10 seconds before record is made. Capillary electrometer with 3-valve amplifier, magnification 490. Time marker gives 0·01 sec. Responses vary in size as electrodes are adjusted between each record.

A. Muscle intact, 2 grm. weight. B. First strip removed, 2 grm. weight. C. Second strip removed, 1 grm. weight; impulses in four regular series. D. Third strip removed, 1 grm. weight; single regular series. (Adrian and Zotterman.)

Observations have been made on afferent nerves leading from sense organs in muscle, skin, and retina.

(*a*) Muscle.—The minute sterno-cutaneous muscle of the frog contains very few sensory endings. It is possible by cutting off part of the muscle to

leave a strip which contains one muscle spindle only, and thus to study the responses of a *single sense organ.* When the muscle is stretched a regular series of impulses are set up, with a frequency of about 30 per second (Fig. 13). Several points of importance must be noted :

1. *Slow Adaptation.*—In the case of nerve fibre, if a constant current of adequate intensity is applied, an impulse is set up when the current is made ; the nerve becomes refractory and gradually recovers to normal, but it does *not* respond again to the presence of the current which is passing through it, though the first application of this current proved an adequate stimulus. It is not known why this happens, but the phenomenon is referred to as "*adaptation*" ; the nerve rapidly becomes accustomed to the constant current, so that it ceases to be an effective stimulus. Similarly, if a sub-minimal constant current is applied to a nerve it can be increased gradually to a great intensity and still fail to excite. The muscle spindle may be

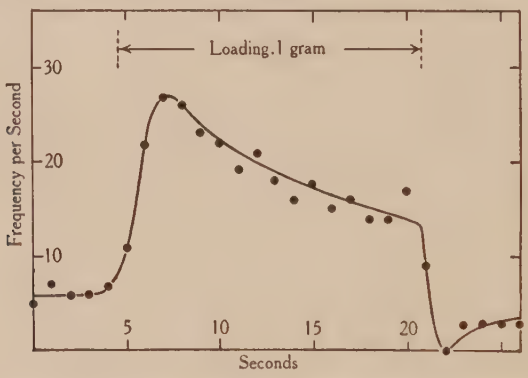

Fig. 14.—Frequency of Responses from Nerve before, during, and after loading Muscle. Note slow adaptation during the period that the stretch is maintained. When the load is removed there is a *complete cessation of* all impulses for a period of 0·75 to 1·5 sec., followed by a gradual return to normal "resting" frequency of response of 3 to 8 per sec. (Adrian and Zotterman.)

regarded as a modified nerve fibre which has not this property of rapid adaptation ; it thus responds to a constant stimulus with a regular series of discharges. The recovery process in end organs is slower than in nerve fibre, so that it discharges less frequently than the maximum rate at which the nerve can transmit impulses ; this ensures that the nerve fibre can recover completely after the passage of each impulse.

2. When the weight is first applied to the muscle the frequency of the discharge is high ; as the stretch is continued, the frequency falls to about half in 15 seconds (see Fig. 14). Adaptation is thus taking place very slowly, and a discharge is still obvious after 10 minutes' stretch. Reflex posture (*e.g.* decerebrate rigidity) depends primarily on afferent impulses from the stretched antigravity muscles ; as these postures are maintained for long periods if the stretching influence persists, it is obvious that the afferent nerve endings in the muscle must be capable of discharging for a long time under constant stimulation.

3. A stimulus which increases slowly is less effective than one which rises rapidly to its final value. Fig. 15 shows that when the intensity of the stimulus increases rapidly a discharge of higher frequency is set up.

(*b*) Skin.—The cutaneous sense organs show very rapid adaptation. If the skin is touched (toe-pad of cat) or hairs are gently moved, a rapid discharge is set up which may only last 0·2 second. One can correlate this with the fact previously mentioned that one soon ceases to be aware of the contact of clothes. The rate of adaptation in pain and pressure sense organs is intermediate between that of muscle spindle and of tactile sense organs. The discharge set up by painful stimuli is not uniformly high, as it would be if pain were due to the excessive stimulation of *any* kind of receptor, as was believed at one time ; the pain discharge, however, is usually one of fairly long duration.

(*c*) Eye.—The impulse discharge from the eye differs little from that of the

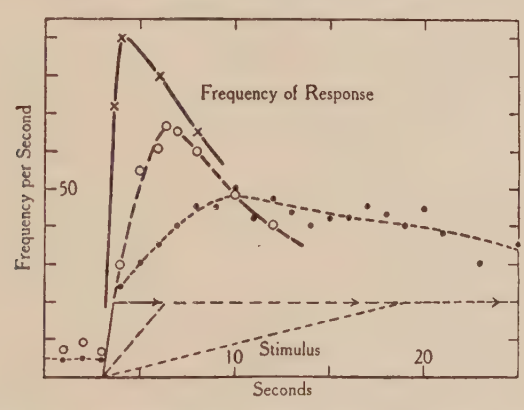

Fig. 15.—Frequency of Responses with various Rates of Loading, showing effects of Adaptation. Maximum tension of muscle 1·3 grm. With very rapid loading maximum frequency is reached about the same moment as the maximum tension. With more gradual loading the maximum frequency is much less and is reached some time before the stimulus is at its full value. (Adrian and Zotterman.)

simpler sense organs. Owing to the decline in the discharge with a constant stimulus, a movement in the visual field will give a stronger excitation than a steady pattern of light and shade ; but the effects of adaptation can be counteracted by movements of the eyes. (Adrian.)

All the sensory impulses from the periphery pass into the posterior nerve roots and thus enter the spinal cord. Before we consider the further course of the somatic afferent fibres, we must deal briefly with two other groups of fibres :

1. **Visceral Impulses.**—Besides the somatic afferent impulses present in the posterior nerve roots, there are less well understood afferent impulses entering from the internal organs and viscera—the so-called "entero-ceptive" impulses. They will not be considered any further here, but will be fully described in connection with the involuntary nervous system (p. 134). But their close anatomical relationship with the somatic afferents must be emphasized, as this fact is used to explain the phenomenon of "referred pain."

2. **Vaso-Dilator Fibres in the Posterior Nerve Roots.**—Stricker showed that stimulation of the peripheral end of the cut posterior nerve roots, *i.e.* towards the body surface, produces vaso-dilatation in the corresponding region of the skin; similar results are obtained if the peripheral sensory nerves are stimulated distally. The fibres concerned have their cell stations in the posterior root ganglia, and not in the spinal cord: if the posterior nerve root is cut *distal* to the ganglion (2, Fig. 16) and a suitable interval is allowed to elapse for the appropriate nerve fibres to degenerate, this vasodilator effect is abolished; if the section is central to the ganglion (1, Fig. 16), the vasodilator fibres survive and the effect persists. The nervous impulse in these experiments is transmitted in the reverse to the normal direction—"antidromically"—to influence the cutaneous blood vessels. Lewis has produced convincing evidence that the dilator fibres in the sensory nerves do not act directly on the skin vessels, but liberate a chemical substance in the skin resembling histamine in its action ("*H*"-*substance*, cf. p. 296) which is responsible for the cutaneous vasodilatation.[1] The stellate ganglion (p. 120) of the cat is extirpated 3 to 4 weeks previous to the experiment to eliminate the sympathetic fibres to the forelimb; stimulation distally of the sensory branches of the median nerve produces flushing of the pads of the foot.

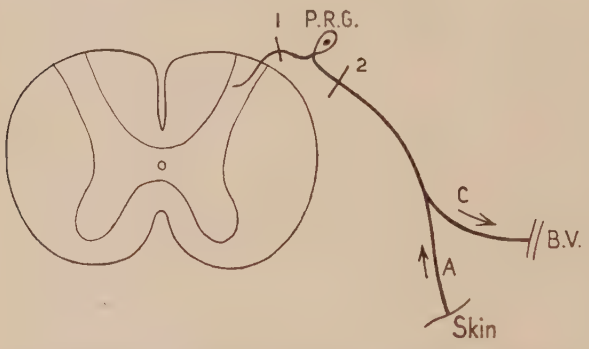

FIG. 16.—Diagram to illustrate the Axon Reflex in the skin.

P.R.G. = Posterior root ganglion; B.V. = Cutaneous blood vessel. (For explanation of letters A, C and numbers 1, 2, see text.)

(i) If the nerve is stimulated for 20 to 40 seconds the intensity of the flush is seen to increase steadily during the period of stimulation to a maximum; it maintains this level and then declines gradually over a period of 5 to 10 minutes. The gradual appearance of the flush and its slow decline suggest the appearance and removal of a dilator chemical substance.

(ii) The circulation in the limb is obstructed; the nerve stimulation is repeated, and the circulatory arrest is maintained for another 5 to 10 minutes, *i.e.* the period during which the dilator effect would normally subside; the circulation is then released. The pad now becomes brightly flushed, and the redness persists for as long as in the previous experiment and then fades: the duration of the fading, measured from the release of the circulation, agrees well with the duration of the fading when the stimulation was carried out with the circulation intact. These observations suggest that during the period of circulatory arrest there was liberated, as a result of antidromic stimulation, a dilator chemical body which accumulated in the tissues. This was only removed by the blood stream after the circulation was restored for a sufficient

[1] Lewis and Marvin, *Heart*, 1927, vol. xiv. p. 27.

length of time. (Similar results are *not* obtained from vasodilator nerves like the n. erigentes.) The vasodilatation in this experiment involves both the capillaries and the arterioles; the "H"-substance dilates the capillaries by a direct action on their wall, but the arteriolar dilatation is probably due to an "*axon-reflex*." This may be defined as a reflex which depends on the *branching of a nerve fibre* (cf. p. 140). The "H"-substance stimulates sensory nerve endings in the skin, and impulses pass along the afferent nerve A (Fig. 16) and then along the branch C' to dilate the neighbouring blood vessels. The sensory fibres which arise from Pacinian and other nerve endings in the skin have been shown to give numerous medullated collaterals to the adventitia of the neighbouring arterioles; it is presumably these fibres which are responsible for the dilator effects just described (cf. p. 292).

The above experiments explain the cutaneous phenomena of *herpes zoster*. In this disease noxious influences, such as inflammation, hæmorrhage, pressure, or poisons, act on the posterior root ganglia or their cranial homologues. The lesions are equivalent to stimulation of the ganglion, and so dilatation of the blood vessels in the corresponding skin area occurs. The "H"-substance not only dilates the minute vessels but also increases their permeability. This leads to exudation of serum and formation of *vesicles* in groups, along the distribution of the posterior nerve roots, or their cutaneous sensory branches.

We may now resume our consideration of the somatic afferent impulses. It is extremely important to recognize that as soon as these impulses enter the spinal cord, *regrouping* takes place. Thus, all forms of touch, whether crude or precise; all forms of temperature, whether extremes of heat and cold, or intermediate grades of temperature; and all forms of pain sensibility come together. The distinction between epicritic and protopathic sensation vanishes, and we recognize only four sensory groups: (1) Touch; (2) pain; (3) temperature; (4) muscle sense ("kinæsthetic" impulses).

To make the position quite clear, a practical illustration may be quoted: If an injury damages the temperature path in the spinal cord, all forms of this sensation are equally affected. By contrast, an injury to a peripheral nerve may result in loss of ability to appreciate temperatures between 24° to 38° C. (epicritic sensibility), while extremes of temperature remain unaffected (protopathic sensibility).

The kinæsthetic impulses can be further subdivided into two groups: (i) some pass up the posterior columns, reach the cerebral cortex, and thus enter consciousness; (ii) others relay in Clarke's column of cells to proceed up the cerebellar tracts to the cerebellum; these of course do not enter consciousness.

It is convenient to summarize at this point the modes in which a posterior nerve root fibre may terminate.

I. In the *grey* matter of the same side.

i. Impulses of pain and temperature, and some impulses of touch end round the cells of the posterior horn of grey matter.

ii. Proprioceptive impulses destined for the cerebellum end round Clarke's column of cells [dorsal nucleus] at the base of the posterior horn.

iii. Some fibres pass directly to the anterior horn cells as, for example, those subserving the knee-jerk.

iv. Impulses from the viscera probably terminate round the lateral column of cells which gives rise to the sympathetic connector fibres.

II. In the corresponding grey matter of the *opposite* side.

III. In the *white* matter.

i. Impulses of muscle sense destined for the cerebrum proceed along large fibres into the posterior columns of the same side.

ii. Short ascending branches of the posterior nerve roots constitute Lissauer's tract at the apex of the posterior horn.

Sensory Paths in the Spinal Cord.—The impulses of *pain*, *temperature*, and a proportion of those of *touch* end, as stated, round the cells of the posterior horn of grey matter. It is probable that around these "intramedullary receptors," as they are called, the regrouping of the impulses already described takes place. From the posterior horn cells a fresh relay arises. The fibres cross to the antero-lateral columns of white matter of the opposite side to constitute the *spino-thalamic* tract (Fig. 17).

It is important to notice that this crossing takes place in close relationship to the central canal of the spinal cord, either in the posterior or anterior commissure. In the lower levels of the spinal cord, these fibres cross transversely in the segment from which they arise. In the higher levels of the cord this crossing becomes increasingly oblique. Thus, in the dorsal region it occupies two or three segments, and in the cervical region four or five segments. It must further be noted that at all levels, the impulses of pain cross most transversely, those of touch most obliquely, while those of temperature occupy an intermediate position.

The fibres which carry impulses from the *deep* structures end, as noted, in two ways:

A. Some fibres terminate round Clarke's column of cells at the base of the posterior horn, chiefly in the thoracic and upper lumbar regions. From this column the *dorsal cerebellar tract* and the *ventral cerebellar tract* arise. These two tracts convey impulses from the muscles, tendons, and joints to the cerebellum, which thus becomes aware of the position of the different parts of the body. It is hardly necessary to add that these impulses do not enter consciousness. The effect of an injury to these cerebellar tracts is to maim the cerebellum, as it is obvious that unless the cerebellum is continually receiving impulses from the deep structures, it cannot carry out its functions of maintaining posture and co-ordinating the activities of muscles. We therefore find the usual symptoms of cerebellar injury such as ataxy, atonia, etc. (These are described more fully on pp. 87 *et seq.*)

Both cerebellar tracts arise from Clarke's column of cells of their own side, and thus convey impulses from their own half of the body to the same side of the cerebellum.

The direct (dorsal) cerebellar tract of Flechsig [*dorsal spino-cerebellar tract*] lies external to the crossed pyramidal tract on the surface of the lateral aspect of the cord. The fibres pass by way of the inferior peduncle of the same side to the posterior part of the vermis.

The indirect (ventral) cerebellar tract of Gowers [*ventral spino-cerebellar tract*] lies in the anterior columns of the cord in the lumbar region. As the fibres ascend, they form a narrow band on the surface of the antero-lateral region of the cord. Most of the fibres do not enter the cerebellum until they reach the superior peduncle and thus pass into the anterior part of the vermis.

B. The other fibres from the deep structures pass up the posterior columns of the spinal cord. In the cervical region the posterior columns are divided

by a well-marked septum containing pia mater into a mesial and a lateral column. The mesial column contains the tract of Goll [funiculus gracilis], while the lateral column contains the tract of Burdach [funiculus cuneatus].

The *tract of Goll* is derived from posterior nerve roots of the lower half of the body and therefore carries impulses from the lower limb and the lower half of the trunk. Every fibre as it enters the posterior columns of the cord " prefers " to take up its position close to the mesial side of the posterior horn. As it ascends the cord, it is gradually displaced inwards from this most favoured position by fibres which have entered at higher levels of the cord. So, as we trace the tract of Goll up, we find that in the lumbar region it lies close to the mesial side of the posterior horn. As it ascends it passes inwards, and in the cervical region occupies the mesial column of white matter on the inner side of the septum of pia mater described above. The tract ends in the nucleus gracilis in the medulla.

The *tract of Burdach* is derived from the posterior nerve roots from the upper limb and upper half of the trunk. It occupies the postero-lateral column of white matter, and ends in the nucleus cuneatus in the medulla.

A further relay of fibres arises in these nuclei, and passes by way of the thalamus to the sensory region of the cerebral cortex. There the impulses enter consciousness and give information of the *position* of the limbs in space, and of the nature of any *passive movement* imposed on any part of a limb. Injury to the posterior columns results in loss of conscious sensation from the deep structures and disturbance of movement (see pp. 38–39, (*b*) i.–iv.). The posterior columns also convey some of the impulses of *touch* from the same side of the body, especially the impulses underlying tactile localization and discrimination ; these touch fibres do *not* relay in the spinal cord but are conveyed to the posterior columns direct to the medulla (Fig. 17).

We can now explain the findings in some diseases of the spinal cord.

(*a*) **Syringomyelia** is a condition of excessive overgrowth of neuroglial tissue accompanied by cavity formation, affecting the grey matter round the central canal of the spinal cord. There is serious involvement of the crossing fibres of pain and of temperature, which decussate in the posterior and anterior commissure, and this leads to loss of these sensations. The touch fibres which cross in this region are likewise destroyed. Touch, as we have seen, has a double path ; some of the fibres ascend the posterior columns, and consequently escape. We thus obtain the characteristic " *dissociated anæsthesia* " of this disease, *i.e.* there is a loss of pain and temperature sensibility, while the sense of touch is retained.

In **Hæmatomyelia,** in which a hæmorrhage suddenly destroys the same region of the cord, similar sensory findings obtain, and the same is the case in *intramedullary* tumours of the cord. The nutritional or *trophic* changes in skin and bone in syringomyelia are due to loss of the protective pain and temperature sensations. Any part that may be injured fails to receive care and attention because no pain is felt. Suppurating whitlows and necroses of bone are common.

(*b*) In **Subacute Combined Degeneration** of the cord, the *posterior* columns are often affected early with the characteristic findings described.

(*c*) In **Hemisection of the Cord** by injury, or by compression from extramedullary growth, posterior column sensibility is lost on the same side

as the lesion, while pain and temperature are lost, and touch blunted on the opposite side (cf. p. 106).

Injury to the *posterior nerve roots* produces the following results in the corresponding segments of the body : [1]

1. Loss of all forms of sensation—pain, temperature, touch, and muscle sense.
2. Loss of muscle tone.
3. Loss of the superficial and deep reflexes.
4. Loss of visceral sensibility.
5. Great clumsiness in the movement of the part, which makes its use almost impossible. This takes place because all parts of the central nervous system—the cerebral cortex and the centres concerned with the reflex control of posture—are deprived of all information from the muscles.
6. Trophic changes.

Tabes.—The essential lesion of tabes is probably a degeneration of the posterior nerve roots central to the ganglion, having, however, a special selective action on those fibres which are destined to ascend the posterior columns.

The consequent clinical manifestations illustrate very well the effects of damage to posterior nerve roots. The resulting phenomena are subjective and objective :

The Subjective phenomena are :

i. " *Lightning pains* " : which come in attacks with intervals of freedom. The pain may be referred to any structure—skin, muscle, or bone, and may vary in intensity from slight discomfort to intolerable agony. It would appear that the first effect of the disease is to set up violent impulses in the pain sensibility fibres in the posterior nerve roots, and the pain felt is referred to the surface of the body.

ii. *Hyperalgesia* is present. Painting the skin with iodine or feeling for bony landmarks as a preliminary to lumbar puncture gives rise to much discomfort. It is not clear why sensations received are magnified in this manner.

The Objective findings are as follows :

1. The fibres conveying pain impulses and those from the deep structures are affected first and to the greatest extent.

(*a*) *Pain* sensibility may be lost, its appreciation is delayed, or it may be inaccurately located. As in syringomyelia, loss of pain sensibility may be responsible for *trophic* disturbances. Many authorities think the *Charcot joint* is produced in this fashion. An injury may be inflicted on a joint, or a mild sprain or subluxation may occur. As no pain is aroused, the condition is neglected, receives no effective treatment, and becomes progressively worse until very considerable deformity results.

The *perforating ulcers* found under the ball of the foot probably arise from neglect of a corn.

The fact that the posterior roots mainly affected in tabes are those supplying the cervico-dorsal and the lumbo-sacral regions of the cord, explains the location of the anæthesia round the anus, over the legs, upper chest, ulnar borders of hands. The involvement of the fifth nerve accounts for the anæsthesia of the central part of the face.

(*b*) The fibres destined to ascend the posterior columns are damaged.

[1] For fuller details see discussion of tabes.

There is loss of sense of position, of passive movement, and of vibration sense in bone, and clumsiness of voluntary movement.

i. Loss of *sense of position* ; with the eyes closed the patient is unaware of the position of any part of his body.

ii. Loss of *sense of passive movement* ; while the eyes are closed, the great toe, for example, may be flexed or extended without the patient's knowledge of the alteration of position imposed on the toe.

iii. Loss of *vibration sense in bone.* After striking a tuning-fork, the handle is placed on some bony prominence. Normally, a sensation is felt which is varyingly described as a "buzzing" or "electrical" sensation. When posterior column sensibility is lost, the patient states that he merely feels a cold object in contact with his skin.

iv. There is considerable disturbance of voluntary movement, illustrating the important general principle that the essential basis of all purposeful and effective motor activity is to be found in accurate sensory information. Normal persons carry out many movements without the aid of the visual sense, being guided by the conscious sensations which reach the sensory cortex *via* the posterior columns. An example, of a homely kind, is the act of fastening a back collar-stud, or standing still while washing the face over a basin. Similarly, in the act of walking, one looks at various surrounding people and buildings, and does not carefully observe the movements of one's legs, and the effectiveness of our progress does not suffer in any way thereby. With loss of the posterior column sensibility, the gait is clumsy ; the patient walks with his legs apart to help compensate for his ataxy. Every phase of each movement is overdone, because the normal sensory impulses which would check the movement are not received. The feet are raised too high and stamped down too forcibly—"stamping gait." The well-known "*finger-nose test*" demonstrates the defect under consideration very well. The patient is asked to place the tip of the forefinger of the outstretched hand on the nose while his eyes are shut. Instead of taking the shortest and most direct route, and readily touching the nose, the finger wanders about aimlessly, and finally alights on the cheek, chin, or neck. The patient is unaware of the position of the nose or the finger, and not knowing what progress the hand is making, it is little wonder that he fails to find his objective.

2. Temperature and touch are affected to a variable extent, but the loss of these sensations is not peculiarly characteristic of the disease.

3. (*a*) It will be shown (p. 51) that postural activity of muscle (muscle tone) depends primarily on the receipt of impulses *via* the posterior nerve roots from the corresponding muscles. If these impulses are not received, loss of tone or diminished tone (hypotonia) results. The muscles are flabby, and the limbs can be placed in unnatural positions, and excessive movement is permitted at the joints without producing discomfort.

(*b*) The deep reflexes (*e.g.* knee-jerk, ankle-jerk) also depend on the integrity of the posterior nerve roots, and so these, too, are lost.

Should the patient close his eyes while standing with the feet together, he sways from side to side, and, if not supported, finally falls to the ground ("Romberg's sign"). This inability to stand may be due to loss of the afferent impulses (which pass in the posterior nerve roots) from the quadriceps to subserve the "stretch reflex" (p. 52), and produce reflex contraction of the quadriceps of a sustained character when the body is in the erect position (cf. p. 53).

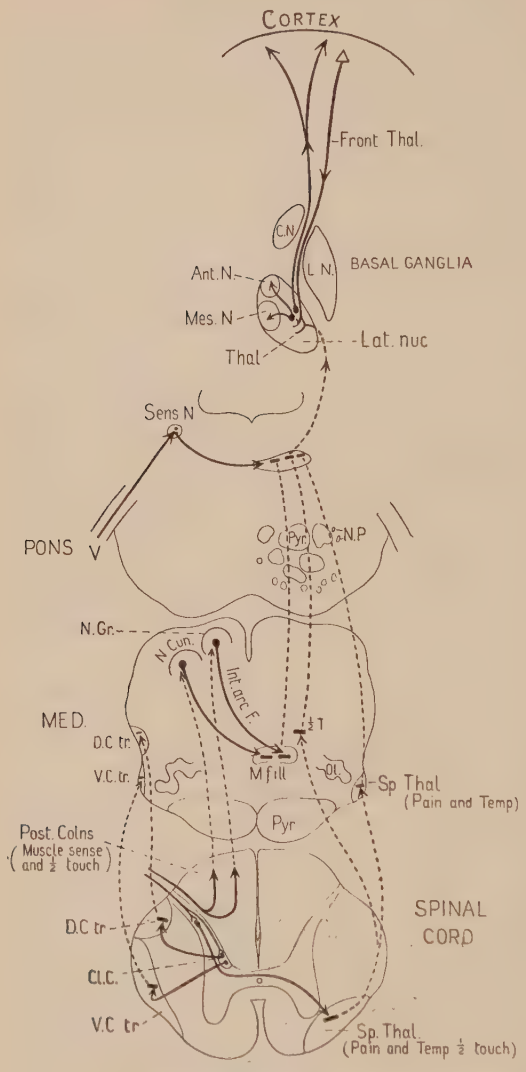

FIG. 17.—Diagram of Course of Sensory Impulses.

Front. Thal. = Fronto-thalamic fibres; C.N. = Caudate nucleus; L.N. = Lenticular nucleus; Ant.N. = Anterior nucleus; Mes.N. = Mesial nucleus; Lat.Nuc. = Lateral nucleus; Thal. = Thalamus; V. = Afferent fibres of fifth nerve; Sens.N. = Sensory nucleus of fifth nerve; N.P. = Nuclei pontis; Pyr. = Pyramidal tract; N.Gr. = Nucleus gracilis; N.Cun. = Nucleus cuneatus; Med. = Medulla; D.C.tr. = Direct cerebellar tract; V.C.tr. = Ventral cerebellar tract; Int.arc.F. = Internal arcuate fibres; M.fill. = Mesial fillet; Ol. = Olivary nucleus; Sp.Thal. = Spino-thalamic tract; ½T. = Half of touch fibres which crossed in the spinal cord; Cl.C. = Clarke's column of cells.

4. The sphincter trouble in this disease results from the loss of visceral sensibility of bladder and rectum. The patient does not know when his bladder is full, and consequently it goes on filling, and becomes excessively distended without arousing any desire to micturate. The heightened pressure in the bladder finally forces the sphincter open, and small amounts of urine overflow at intervals (see also p. 144).

Sensory Paths in the Brain Stem.—1. TRACTS OF GOLL AND BURDACH.—In the lower medulla, the posterior columns widen, and grey matter appears in their substance in which the fibres end. The tract of Goll ends in the nucleus gracilis, and the nucleus cuneatus receives the tract of Burdach. From the small cells forming these nuclei a fresh relay of fibres arises, and sweeps forward across the middle line as the *internal arcuate* fibres to form a bundle of fibres known as the *mesial fillet* [mesial lemniscus], which lies near the middle line and behind the pyramid. The decussation is often called the sensory decussation, or the decussation of the fillet. It may be noted that the fibres from the lower limb (from nucleus gracilis) cross at a lower level in the medulla than those from the arm (from nucleus cuneatus). Some fibres

from the nuclei pass *via* the inferior peduncles, mainly to the opposite side of the cerebellum (cf. p. 86).

The mesial fillet at this stage is only conveying the impulses carried in the posterior columns, *i.e.* muscle sense and some touch impulses (those for tactile localization and discrimination).

2. The Spino-Thalamic Tract breaks up in the medulla into two bundles. The fibres carrying pain and temperature remain on the surface of the medulla external to the olivary nucleus, where they mingle with the ventral cerebellar tract. The fibres of touch diverge from these (being anxious, it would seem to rejoin the rest of the touch fibres, which are lying in the mesial fillet), and lie in the formatio reticularis of the medulla, dorsal and slightly lateral to the mesial fillet. In the pons they join the mesial fillet, and by this time the pain and temperature fibres have passed inwards sufficiently to join the main sensory path too. The mesial fillet thus enlarged is now carrying all the impulses from the opposite side of the body, below the neck (Fig. 17).

3. Afferent impulses from the *face* enter by the fifth nerve, and end in the principal sensory nucleus in the pons and in the long descending root and adjacent grey matter which extend down to the upper cervical region of the spinal cord. From this long column of grey matter a fresh relay arises which crosses the middle line to complete the mesial fillet. It has recently been suggested that the fibres of the ophthalmic division of the fifth nerve end in the lowest part of the spinal part of the descending root; the maxillary division ends in the middle part of the root, while the superior part of the nucleus receives the inferior or mandibular division of the nerve. In other words, the face is represented "upside-down" in the nucleus. The mesial fillet receives accessions of fibres from other sensory cranial nuclei, particularly the vagus (from the upper air passages), the dorsal nuclei of ix. and vii. (taste fibres), and the vestibular division of viii. (from the labyrinth).

4. The mesial fillet in the midbrain lies in the tegmentum behind the substantia nigra and close to the middle line. It is now conveying the sensory fibres just enumerated in addition to cutaneous and deep impulses from the whole of the opposite side of the body. The mesial fillet passes through the posterior part of the internal capsule to reach the optic thalamus.

The Optic Thalamus [Thalamus].—This large ganglion represents the highest sensory centre of the lower animals. In man, however, most of its functions have been taken over by the cerebral cortex.

The thalamus consists of two main parts:

1. The *lateral* nucleus which is continued backwards into the pulvinar and the external geniculate bodies. This nucleus serves solely as a relaying and regrouping station.

2. The *mesial* and *anterior* nuclei which together form the "essential organ of the thalamus." It is very important to note that here certain elements of sensation actually enter consciousness.

Connections of the Thalamus.—The thalamus receives the following tracts:

1. Mesial fillet (including vestibular and taste fibres).
2. Optic tract (p. 46).
3. Olfactory tract.
4. Cerebellar fibres from the dentate nucleus of the opposite side *via* the superior cerebellar peduncle and the red nucleus (p. 86).

(Note that the auditory fibres do not relay in the thalamus.)

Fibres pass out of the thalamus to mingle in the internal capsule to reach the following structures :

1. The corpus striatum : the fibres are believed to pass first to the globus pallidus and then reach the putamen and the caudate nucleus.

2. The cerebral cortex : by means of a series of radiations to the frontal, parietal, and occipital convolutions, and probably to the hippocampal region too.

Descending fibres are said to pass from the frontal lobes to the thalamus, constituting the cortico-thalamic tract.

Functions of the Thalamus.—1. The thalamus is an important relay station. The sensory tracts ending in the lateral nucleus are regrouped and redistributed in two directions, namely, to the sensory cortex and to the " essential organ " of the thalamus. The cerebellar fibres which the thalamus transmits to the cortex are of the greatest importance. It is by this means that the cerebellum guides and controls the cerebral cortex when it is carrying out volitional movement. If this connection is severed, very serious functional disturbances arise, which bear a close similarity, as would be expected, to the effects of injuries to the cerebellum itself (cf. p. 98). The cerebellum is a peculiar organ in this respect. Whether the lateral hemisphere of the cerebellum itself, or its afferent connections, or its outgoing paths are damaged, the functional changes are very much alike. Each cerebellar hemisphere (*e.g.* right) *via* the opposite (left) thalamus guides the opposite (left) cerebral cortex. The cerebral cortex *via* the pyramidal tracts influences the opposite muscles, *i.e.* of the right side. An injury to the thalamus therefore produces signs of cerebellar disturbance on the opposite side of the body. These consist of weakness and slowness of movement ; ataxy during voluntary movement (cf. p. 89) ; and diminished muscle tone. The superficial reflexes and the plantar response are normal on the affected side of the body. The cerebral cortex, no longer checked by the guiding cerebellar impulses, gives rise to involuntary spontaneous movements, either choreiform or athetotic. (The nature of these movements is discussed on p. 92).

2. As stated, the " essential organ " of the thalamus is a centre for recognition of certain " crude " sensations. The sensory cortex is responsible for the finer discriminative aspects of sensation. These functions of the thalamus are best studied when its connections with the cortex are severed. The cortico-thalamic fibres—which normally inhibit thalamic activity and prevent thalamic sensations from occupying consciousness to any great extent—are thus cut. The functions of the thalamus are thus revealed as they exist when freed from cortical control.

(1) Light touch (*e.g.* cotton-wool), tactile localization, and discrimination are not recognized.

(2) Painful stimuli are felt and arouse excessive discomfort. A stimulus of an unpleasant order, if felt, produces *more* pain on the affected than on the normal side.

(3) Hot and cold are recognized. There is a parallel overaction to pleasurable stimuli. Warmth applied to the skin, or tickling, or erotic stimuli excite an unusual degree of pleasurable emotion.

(4) Movements at joints are only recognized if they are of considerable amplitude.

In other words, pain, hot, cold,[1] and gross movements are recognized. The emotional accompaniment of the sensations—pleasure and pain—is accentuated. In the intact body these abnormal emotional accompaniments are damped down by the activity of the cortico-thalamic fibres.

Thalamic Syndrome (Roussy).—This syndrome is found when a lesion isolates the thalamus from the cerebral cortex. All the symptoms are found on the opposite side of the body.

1. Weakness, ataxy, choreic, and athetotic movements: these are attributed to damage to the cerebellar fibres which pass through the thalamus to the cerebrum.

2. Considerable loss of discriminative sensation, with overaction to pain and temperature.

3. "Spontaneous" pain may occur. This is difficult to interpret. It may conceivably be due to great exaggeration of unpleasant feeling-tone for some slight stimulus.

4. If the adjacent pyramidal tracts escape, the plantar response is normal.

If the lesion is *subthalamic* in level, pain and gross temperature sensibility are lost too. No lesion of the sensory paths above the thalamic level can affect pain sensibility, which enter consciousness in the thalamus itself. Lesions of the posterior part of the thalamus may affect the visual path.

The Sensory Cortex.—The region of the cerebral cortex concerned with the appreciation of the discriminative aspects of the "general body sensations" is much more extensive than used to be thought. The sensory cortex comprises the post-central gyrus, the superior parietal lobule, and part of the supramarginal and angular gyri—in other words, the greater part of the surface of the parietal lobe. Recognition of pain, temperature, and gross movements occurs at the thalamic level. The sensory cortex endows the sensations with definite discriminative faculties (Head and Holmes).

1. Differences in the relative *intensity* of different stimuli are recognized. Heat is not merely distinguished from cold, but warm objects are distinguished from warmer, cold from colder, rough from rougher, and so forth.

2. There is recognition of *spatial relationships*. The thalamus becomes aware that a stimulus is applied to the body, but gives no precise information concerning the spatial qualities of the stimulus. The sensory cortex locates the precise point stimulated -i.e. *tactile localization*. It can distinguish two points of a compass when close together as two distinct stimuli—i.e. *tactile discrimination*. Lastly, the extent and direction of small joint displacements can be estimated accurately. The relations of a stimulus in one, two, or three dimensional space are clearly defined.

3. Appreciation of *similarity and difference* in external objects brought in contact with the surface of the body (without the aid of visual impressions) is one of the highest functions of the sensory cortex. Differences and similarity of size, weight, form, and texture are thus recognized. This function includes what is usually called *stereognosis*—the ability to recognize the nature of common objects placed in the hand without looking at them. Stereognosis is a peculiarly complicated function. It demands perfect reception of stimuli

[1] The similarity between these sensations and "protopathic sensibility" in the skin is apparent; Stopford (*Brain*, 1927, vol. l. p. 391) has, in fact, suggested that protopathic sensibility proceeds without rearrangement up the cord and brain stem to end in the thalamus.

from the object, giving detailed and accurate information about all its properties. These sensations are apparently synthesized in the cortex and compared with previous similar sensory memories. An object is thus recognized as half a crown and distinguished by the presence of the milled edge (which has been felt for) from a penny piece.

It is said that the post-central gyrus is particularly concerned with " similarity and difference " ; the anterior region of the sensory cortex with " spatial relationships " ; and the lower and posterior part of the parietal lobe with " intensity " of stimuli. Some degree of representation of the different regions of the body in special areas is present in the post-central gyrus. The arrangement is similar to that present in the motor cortex (p. 70). The leg is represented highest up, then trunk, arm, and face in descending order.

In lesions of the sensory cortex the patient's complaint is of clumsiness and " uselessness " of the affected side. This again emphasizes the overwhelming importance of proper sensory guidance of the motor areas of the brain. It is possible, too, that not only is the extent of movements recognized in the sensory cortex, but memories of the *sequence* of movements, or the pattern of voluntary movements, are stored in the cortex too. This fund of information is of the greatest value when movements which have previously been carried out are repeated (see also p. 68).

It is clear, too, that no gross forms of anæsthesia can be expected in lesions of the cortex, and that casual examination of the sensory nervous system will reveal no abnormality. It is essential that the patient be tested for stereognosis. This is found defective almost constantly. Tactile localization and discrimination, or the power to distinguish between slightly differing weights, will not be as precise as on the normal side. Prolonged examination at one time must be avoided, as the sensory cortex fatigues readily.

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The Auditory Path.—The cochlear division of the auditory nerve arises from cells of the ganglion of the cochlea in the inner ear, and passes to the medulla dorsal to the restiform body. Here it ends in two nuclei—the ventral cochlear nucleus, between the two divisions of the nerve, and the dorsal cochlear nucleus or tuberculum acusticum, which lies on the dorso-lateral aspect of the restiform body. From these cell stations a fresh relay of fibres arises.

1. From the ventral nucleus a band of transversely running fibres—the *trapezium*—arises, which crosses to the opposite side about midway between the anterior and posterior aspects of the pons. The fibres of the trapezium may or may not relay in two nuclei which lie in its substance, *i.e.* the superior olive and the trapezoid nucleus.

2. From the dorsal nucleus the medullary striæ, or *striæ acusticæ*, arise,

which cross the midline in the floor of the fourth ventricle and then turn sharply forwards in the raphe to join the trapezium. The united fibres then turn upwards external to the mesial fillet as the *lateral fillet* [lateral lemniscus].

3. It is not correct, however, to describe all the fibres as crossing to the opposite side. The decussation is only partial, like that of the optic nerve fibres (*q.v.*). Some of the fibres of the trapezium and medullary striæ pass up the lateral fillet of their own side (see Fig. 18).

In the midbrain the lateral fillet turns sharply backwards to end in the inferior corpora quadrigemina [inferior colliculi] and in the internal geniculate body. The two internal geniculate bodies are united by fibres running through the optic chiasma and forming *van Gudden's commissure.*

From these centres a fresh relay of fibres arises which passes as the auditory radiation behind the posterior limb of the internal capsule to end in the temporal lobe, especially the superior temporal gyrus. Around this *auditory* centre there develops an *auditory-psychic* centre in which is appreciated the nature of auditory stimuli. Thus in the course of time when we hear the sound of a whistle we associate it at once in our mind with a policeman, or a train moving out of a station, etc. When the significance of common sounds can no longer be appreciated, a condition of *auditory agnosia* is said to exist. In the first and second [superior and middle] temporal convolutions on the left side is an area in which the sounds employed in speech are understood, and this constitutes the *auditory speech* centre (p. 95).

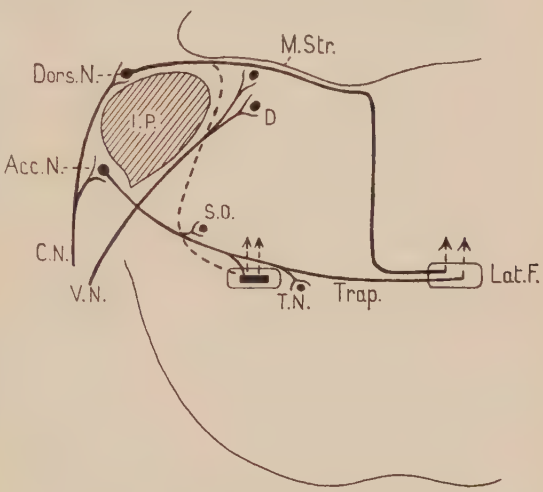

FIG. 18.—Diagram of Auditory Path.

C.N. = Cochlear Nerve; V.N. = Vestibular nerve; Dors.N. = Dorsal nucleus (tuberculum acusticum); Acc.N. = Accessory (ventral) nucleus; M.Str. = Medullary striæ: S.O. = Superior olive: T.N. = Trapezoid nucleus; Trap. = Trapezium; Lat.F. = Lateral fillet.

Lesions of one temporal lobe never cause deafness, because each ear is bilaterally represented in the cortex. Deafness from a lesion of the brain stem is rare, and can only occur when a lesion of the central part of the pons destroys the trapezium or involves both lateral fillets.

Two types of unilateral deafness may be recognized:

1. *Nerve* deafness, from damage to the cochlea or the cochlear nerve in any part of its course.

2. *Middle ear* deafness: from damage to the bony ossicles.

Tests.—RINNE'S TEST.—Normally a tuning-fork in vibration, when applied to the mastoid process until it is no longer audible, will still be heard

when presented at the external auditory meatus, *i.e.* air conduction of sound is better than bone conduction. In *nerve* deafness, hearing may be greatly diminished, but air conduction is still better than bone conduction. In middle ear deafness, as the ossicles are damaged, air conduction is impaired and becomes less acute than conduction by bone.

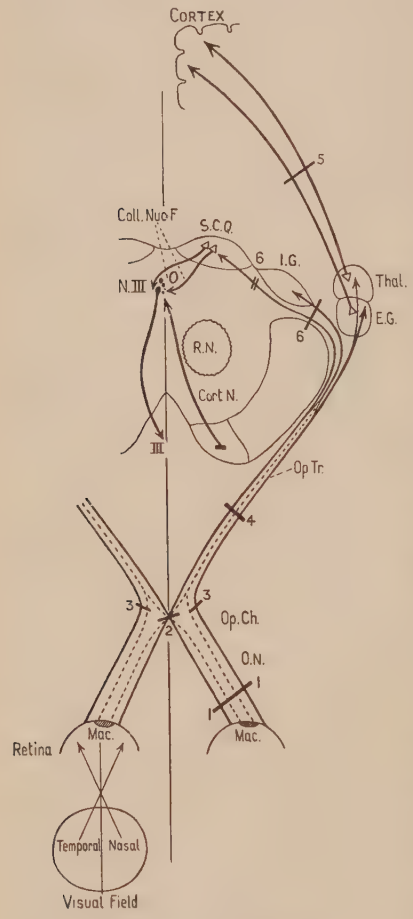

FIG. 19.—Diagram of Visual Path.

Mac. = Macula ; O.N. = Optic nerve ; Op.Ch. = Optic chiasma ; Op.Tr. = Optic tract ; N.III. = Nucleus of third nerve ; III. = Issuing fibres of third nerve ; R.N. = Red nucleus ; S.C.Q. = Superior corpora quadrigemina ; Coll. Nuc.F. = Colliculo-nuclear fibres ; I.G. = Internal geniculate body ; E.G. = External geniculate body ; Thal. = Thalamus (pulvinar) ; Cort.N. = Cortico-nuclear fibres (from frontal lobes to third nerve nucleus). For significance of numbers 1–6, see text.

WEBER'S TEST.—If a tuning-fork in vibration is applied to the forehead in the middle line, it is heard best on the sound side in nerve deafness, and best on the affected side in middle ear deafness.

The Visual Path.—The visual fibres arise in the layer of nerve cells in the retina and pass backwards along the optic nerve to the optic chiasma. Partial decussation takes place, the fibres from the nasal sides of the retinæ cross, and those from the temporal side of the retinæ remain uncrossed. The left optic tract therefore conveys fibres from the left halves of both retinæ. Each half of the retina receives light rays from the opposite half of the field of vision. The left optic tract corresponds, therefore, to the right or opposite half of the field of vision. The fibres from the macula lutea (yellow spot), or region of most precise vision, behave in exactly the same way. The fibres from the nasal sides of both maculæ cross, and those from the temporal sides remain uncrossed (Fig. 19).

The optic tracts thus constituted wind round the outer side of the crura cerebri and end partly in the superior corpora quadrigemina [superior colliculi], and partly in the pulvinar or posterior part of the thalamus [1] and in the adjacent external geniculate body. The superior colliculi serve as a centre for *visual reflexes*. From the thalamus a fresh relay arises which passes back in the optic [thalamo-occipital] radiation to the occipital cortex. The fibres

[1] Recent work suggests that none of the fibres of the optic tract pass directly to the thalamus.

pass through the internal capsule behind the fibres for common sensation, and then pass deep in the substance of the temporal lobe round the outer surface of the lateral ventricle to reach the "half-vision centre" in the occipital lobe. It is so called because, like the optic tract, each occipital centre represents the opposite half of the field of vision. At the extreme *pole* of –*e.g.* the left—occipital lobe, the left halves of both maculæ are represented—i.e. *central* vision. On the inner side of the occipital lobe, above and below the calcarine fissure (cuneus and lingual gyrus respectively), peripheral vision is represented—*i.e.* the left halves of both retinæ, or the right half of the peripheral field of vision. Furthermore, above the calcarine fissure (cuneus), the upper halves of the retinæ (lower halves of the field of vision) are represented; below the calcarine fissure (lingual gyrus), the lower halves of the retinæ (upper halves of the field of vision) are represented.

It is worth remembering that the occipital pole is supplied by the middle cerebral artery, and the inner surface of the occipital lobes is supplied by the posterior cerebral artery. Vascular lesions may therefore destroy central vision, leaving peripheral vision intact, or *vice versa*.

Around the visual centre (where objects are seen) is an association centre or *visuo-psychic* area situated on the outer surface of the occipital lobe. Here the nature of objects seen is recognized, *e.g.* a pencil, or paper, or ball is recognized as such. When this function is lost, *visual agnosia* is said to be present.

The Light Reflex.—There may be special thick fibres from the retina subserving the light reflex, and thinner fibres destined to be relayed to the cortex (Monakow). The nervous arc employed by the light reflex is probably as follows: The afferent fibres enter the superior colliculi from the optic tracts. Here a new relay arises—the *colliculo-nuclear* fibres, which cross both in front and behind the aqueductus Sylvii to reach the most anterior part of the third nerve nucleus. These fibres are probably mingled with the tecto-spinal tract, which is destined to end in the spinal cord. As the fibres from each retina reach both optic tracts and both superior colliculi, shining light on one eye causes constriction of both pupils (*consensual* light reflex). The fibres of the third nerve relay in the ciliary ganglion and pass in the short ciliary nerves to the eye (Fig. 19).

Convergence-Accommodation Reaction. — During accommodation, the ciliary muscle (on both sides) contracts, the suspensory ligament of the lens is relaxed, and the anterior surface of the lens becomes more convex. At the same time, the eyes converge from contraction of both internal rectus muscles, and the pupils are constricted. Convergence-accommodation is to some extent a willed movement, as the object must be definitely looked at before it occurs. It is believed that visual impulses pass up to the thalamus and thence to the occipital cortex and are relayed to the frontal lobes. Fibres arise here which descend in the genu or anterior limb of the internal capsule to reach the inner part of the pes pedunculi. These *cortico-nuclear* fibres then turn abruptly backwards through the mesial fillet to the opposite side, to end in the third nerve nucleus which supplies all three muscles mentioned (see Fig. 19).

Argyll Robertson Pupil.—This term is applied to describe a condition in which the pupillary constriction in response to light stimulus is absent or

notably diminished, while the sphincter pupillæ still contracts during convergence-accommodation. From the description given above, it is clear that fibres subserving the light reflex alone are present in the part of the optic tract entering the superior colliculi, in the superior colliculi themselves, and in the colliculo-nuclear fibres (the fibres subserving accommodation pass up to the cortex) ; the third nerve is the final common path for both reactions We therefore find the Argyll Robertson pupil associated with lesions in the vicinity of the aqueductus Sylvii and the superior colliculi. As syphilis of the nervous system commonly affects this region, this sign is very frequently found in this condition. The Argyll Robertson pupil has been produced experimentally by bilateral section of the optic tract fibres which enter the superior colliculi (6 in Fig. 19).

The following definitions may help us to understand the effects of the commoner lesions of the visual tracts :

Hemianopia : blindness of half the visual field from causes other than retinal.

This may be :

i. Bitemporal or binasal, *i.e.* loss of both temporal or both nasal fields of vision.

ii. Homonymous : loss of the right or the left halves of both fields of vision.

iii. Quadrantic : blindness of one quadrant only.

A lesion of the central part of the optic chiasma (2) (*e.g.* from pituitary tumours) where the fibres from the nasal side of both retinæ cross, causes bitemporal hemianopia. A lesion of the outer margins of the chiasma (3, 3) may damage the fibres from the temporal sides of the retinæ, and cause binasal hemianopia. Any lesion of the optic nerve, chiasma, or tracts up to the point where the fibres for the superior colliculi leave (1, 4), produces loss of the light reflex from the blind side of the retina. A lesion of the external geniculate body, thalamus, optic radiation (5), or occipital cortex produces loss of sight, but the light reflex from the blind side of the retina is retained. A lesion of the optic tracts (4), or their continuation to the cortex (5), causes homonymous hemianopia : *i.e.* a lesion to the left tract or the left visual centre causes loss of the right halves of the field of vision in both eyes.

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The Taste Path.—The anterior two-thirds of the tongue are supplied by the lingual nerve. Fibres carrying taste impulses leave the lingual nerve to enter the chorda tympani, and reach the facial nerve in the aqueductus Fallopii. Their cell station is situated in the geniculate ganglion. The fibres enter the pars intermedia to reach the brain stem and end in the dorsal nucleus of the seventh nerve.

From the posterior third of the tongue, the taste fibres pass along the glosso-pharyngeal nerve, to their cell station in the petrous ganglion, and thence to the dorsal nucleus of the ninth nerve.

It used to be stated that all the fibres of taste passed through the Gasserian ganglion [semilunar ganglion] and entered the brain in the fifth

nerve. According to Cushing, removal of the Gasserian ganglion [semilunar ganglion] never causes any loss of taste over the posterior third of the tongue. After the operation, taste over the anterior two-thirds is lost, but this is said to be of a temporary character, and soon passes off. This transient loss of taste is attributed to the post-operative degeneration and swelling of the fibres of the lingual nerve which have their cells of origin in the Gasserian ganglion. The taste fibres which are carried as " passengers " in the lingual nerve are temporarily pressed on and their conductivity is impaired for a short time. As the lingual nerve fibres atrophy, the fibres of taste recover and regain their function.

From the dorsal nuclei of the seventh and ninth nerves a second relay of fibres arises which probably crosses the middle line to join the mesial fillet of the opposite side (p. 41). The fibres may relay in the thalamus and ultimately end in the hippocampal gyrus, which is the cortical centre for taste and smell.

In irritant lesions of the uncus, hallucinations of taste and smell occur associated with a dreamy state which persists momentarily and then passes off (" uncinate fits ").

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MUSCLE TONE AND REGULATION OF POSTURE

Decerebrate rigidity—Levels of trans-section—The reflex arc—Decerebrate rigidity in man—Myotatic (stretch) reflexes—Relation to stepping—Properties of posturing muscle—Metabolism—Unfatiguability—Shortening and lengthening reactions—Peripheral mechanism of posture—Types of skeletal muscle fibres—Rôle of sympathetic—Regulation of posture.

Muscle Tone.—*Tone*, or *tonus*, is one of the most misused terms in physiology, and a sharp definition is essential. We talk of the tonic action of the vagus when we simply mean that the vagus is constantly acting and reining in the heart. Tone in muscle is usually defined as " a state of slight constant tension which is characteristic of all healthy muscle, and which serves to obviate the muscle taking up slack when it enters upon its contraction." This explanation is inadequate : tone is not uniformly distributed in all muscles, and the latency of the *toneless* frog nerve-muscle preparation is less than one-hundredth of a second.

Decerebrate Rigidity.—A great deal of light is thrown on the subject by studying a mammalian preparation in which most of the anterior part of the brain is removed by a trans-section through the hinder part of the mid-brain. It is then found that all four limbs are rigidly extended, the jaw is closed, the head is raised, the tail is lifted, and the back is arched. If one of the limbs is handled, the muscles are found to be firmer than normal, and it is difficult to alter the position of the limb ; it is obvious that we are dealing here with muscle tone in a heightened form, but so far we have been given no clue as to its significance. If, however, instead of allowing the preparation to lie on its side on the table, we stand it on its legs, we find that it remains standing. Muscle tone apparently enables the preparation to stand, and we get an inkling as to the meaning and purpose of tone—it

enables the animal to maintain a position or "*posture*." This position of standing, we shall see, is maintained reflexly, so we can define muscle tone as being concerned with, and being the basis of, reflex posture. We are thus introduced to a somewhat unfamiliar type of reflex. We are all acquainted with reflex movements; here we are considering reflex maintenance of positions. It is just as purposive and co-ordinated as any reflex we know of. All the muscles which have to counteract gravity and prevent the animal from sinking to the ground are contracted, and we therefore call the muscles which are found contracted in this preparation the "*antigravity muscles*." Their antagonistic muscles are found reciprocally inhibited.

The condition described is known as "*decerebrate rigidity*," but before we analyse it further, we must study the exact levels of the trans-sections which are necessary for producing the condition.

Levels of Trans-section.—Rigidity develops when the coronal section

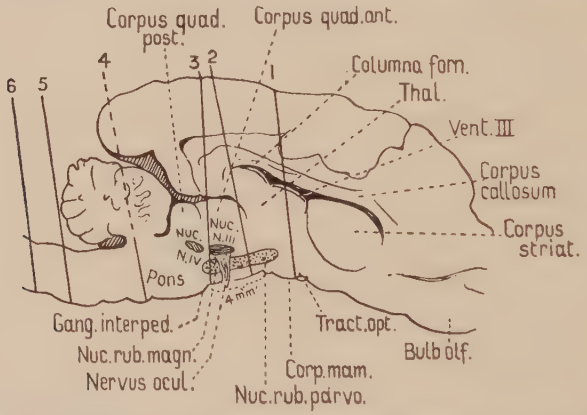

FIG. 20.—Diagram showing the various Levels of Trans-section (cat) of the Brain Stem used in His and Rademaker's analysis of Regulation of Posture (see text).—After MAGNUS, *Körperstellung*.

passes through the midbrain in a plane which passes through the superior corpora quadrigemina dorsally, and cuts off the greater part of the red nucleus from the body [1] (Plane 3, Fig. 20). If the trans-section passes *above* (cephalic to) the red nucleus, tone remains normal (Plane 2, Fig. 20). Only if the red nucleus itself is injured or its efferent fibres severed does rigidity appear. Rigidity persists as the plane of the trans-section passes caudally through the pons and upper medulla. When Deiters' nucleus is cut out, flaccidity develops (Plane 5, Fig. 20). Clearly the brain stem centres responsible for decerebrate rigidity lie in the medulla and possibly in the pons too; the principal nucleus concerned is probably Deiters' nucleus [lateral vestibular nucleus].

[1] The caudal third of the red nucleus (n. magnocellularis) which gives rise to the rubro-spinal tract is the part of the nucleus which must be injured to produce decerebrate rigidity (see p. 112 and Fig. 20); injury to the more cranially situated n. parvocellularis (*e.g.* section through Plane 2, Fig. 20) does not affect muscle tone. When the term "red nucleus" is used in the text, the n. magnocellularis is usually being referred to.

The Reflex Arc.—If the posterior nerve roots coming from one limb are severed, the rigidity at once disappears in that limb only. Obviously, then, the rigidity is reflex in character. If the limb is skinned, rigidity still persists. We may conclude that the afferent impulses responsible for maintaining the position must come from the *deep* structures, muscles, tendons, etc. The proof is as follows. In the limbs, the extensors of the thigh are in a state of marked tonic contraction. All the nerves in the limb can be cut except the nerve to the quadriceps, and tone in that muscle persists. This nerve, of course, contains afferent fibres from the muscle spindles and tendon organs as well as motor fibres, and so long as the fibres to and from the muscle are intact, tone is present. The afferents from the quadriceps in the cat reach the cord *via* the posterior roots of L5, 6. If these two roots are cut, tone vanishes from the muscle, even if every other nerve in the limb is intact. It is clear, therefore, that the tone of any muscle depends primarily on impulses arising in the muscle itself. The reflex is set up by the slight *stretch* to which the antigravity muscles are subjected : if the quadriceps is detached from its attachment and thus no longer subjected to stretch, tone in the muscle at once disappears (*v. inf.*).

These afferent fibres ascend the cord in the antero-lateral columns[1] of the white matter, and section of these columns abolishes tone below the level of the lesion. The fibres pass up to Deiters' nucleus in the upper medulla (and perhaps to the nuclei pontis). The efferent arc is probably mainly along the vestibulo-spinal tracts to the anterior horn cells of the cord. The extensor muscles are intensely stimulated, and the antagonistic muscles are reciprocally completely inhibited.

Decerebrate Rigidity in Man.[2] Decerebrate rigidity has been described in man. The position of the leg is extension at the knee and plantar flexion (" extension ") at the ankle, and is identical with that of the experimental animal. The position of the arms is different. They lie across the chest, semiflexed at the elbows, the forearm slightly pronated, and the wrists and fingers flexed. It is not very surprising that the arm adopts a different attitude in man, for we use our arms in a different way from that in which an animal uses its fore-limbs. It will be seen that the position of the limbs is identical with that which follows injuries to the pyramidal tracts in man. In those cases, too, the abnormal position and coincident abnormal distribution of tone are due to release of function in the lower brain-stem nuclei (p. 76). To put the matter simply, the higher parts of the brain down as far as the red nucleus tend to keep the limbs in the normal position, and the muscles show normal tone. The pontine and medullary centres, when they are allowed to act independently by removal of the higher parts of the brain, reflexly maintain a somewhat exaggerated or caricatured posture of standing.

Myotatic or Stretch Reflexes.—A great deal of light is thrown on the mode of production of decerebrate rigidity and on the physiology of muscle tone by the studies of Liddell and Sherrington on the *myotatic* or *stretch* reflexes. In the decerebrate animal the quadriceps muscle is isolated from its attachment and fixed by means of a steel hook in the patellar tendon to a stiff spring, to which a light lever is attached, the movement of which is

[1] Not in the posterior columns ; section of the posterior columns does not affect decerebrate rigidity.

[2] See Fig. 27, p. 62.

recorded photographically on a moving plate. The record obtained is an *isometric* one (when the muscle contracts it is only permitted to shorten to a minimal degree), so that the tension developed by the fibres is shown. The hind limbs and pelvis are firmly fixed to a rigid table, which can be lowered to any degree and at any rate, and the muscle can thus be subjected to carefully controlled stretch.

1. In the case of *paralysed* muscle (motor nerve cut), a small increase in tension results from the stretch ; the curve obtained resembles that given by stretched indiarubber (Fig. 21).

2. If the nerve supply is intact a different curve is obtained : a much greater tension is developed, the extent of which depends on the degree of stretch. The response is reflex in character, because on section of the posterior nerve roots carrying the afferents from the muscle the curve of paralysed muscle is obtained. A stretch of several millimetres (*i.e.* less than 1 per cent.

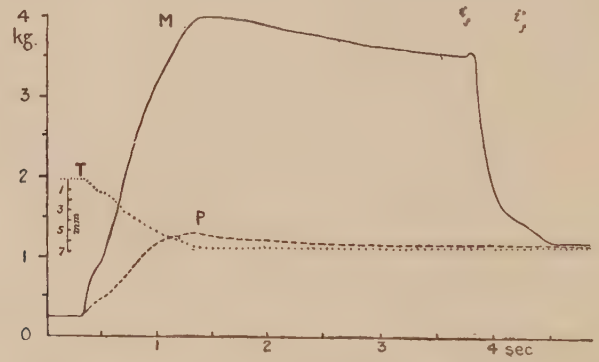

Fig. 21.—Response of Intact and Paralysed Muscle to Stretch.

Knee Extensor Muscle.—T=Stretch of 6·5 mm. applied; M=Innervated, P=Paralysed muscle; *i* to *i'*=Inhibitory afferent nerve stimulated, which abolishes the stretch reflex and tension in M falls to level of P. Time in seconds. Myograph multiplies tendon movement 62 times. (Liddell and Sherrington, *Proc. Roy. Soc.*, 1924.)

of the initial length of the muscle) may produce a reflex contraction of 2 kg. tension. As the stretch is applied, rapid development of tension occurs. With an evenly applied stretching force, an increasing number of receptors in the muscle are brought into action, and reflexly an increasing number of muscle fibres contract ; if the stretch is irregularly applied the increase in tension is also uneven. While the stretch is maintained, a more or less steady tension is kept up without fatigue for as long as half an hour. The plateau of the curve usually tends to diminish in height a little at first, and then usually maintains a steady level. When the stretch ceases, the muscle relaxes. A muscle thus reflexly responds to stretch by active contraction, and this tends to antagonize the stretching force, produce equilibrium, and prevent further elongation of the muscle. The *source* of the reflex is the muscle itself ; it can still be obtained after the tendon is anæsthetized with novocain, or after cutting away the tendon and attaching the muscle direct to the myograph. If the quadriceps is divided into four segments, the part stretched alone contracts ; the response is thus intensely *local* in character. The

stretch reflexes are characteristic of the *antigravity* muscles; stretch of the flexor muscles may give rise to a short-lived response, but never to a maintained contraction. The stretch reflexes are obtained after section of the eighth nerves, in the thalamic and probably in the normal animal. Decerebrate rigidity may be regarded as made up of a harmonious group of stretch reflexes: when the decerebrate animal is put on its legs, the knees tend to bend under the weight of the body; the consequent stretch of the quadriceps reflexly sets up its contraction, which is maintained so long as gravity is acting; and similarly for the posterior neck muscles and the other antigravity muscles.

If an inhibitory afferent nerve is stimulated (*i.e.* any sensory nerve in the same limb), or if the antagonistic flexor muscle is pulled on, the quadriceps relaxes, although the stretching force is still applied to it (Fig. 21); similarly,

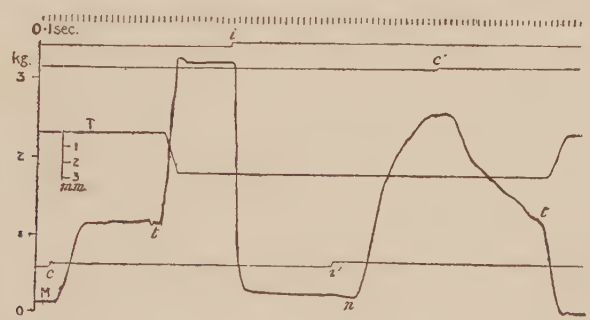

Fig. 22.—Stretch Reflex of Contracting Muscle.

Knee Extensor Muscle.—c to c' = Stimulation of afferent nerve on opposite side (peroneo-popliteal) evoking reflex contraction (crossed extensor reflex). At t, 2·5 mm. stretch applied (shown on line T), evoking marked stretch reflex from the contracting muscle. i to i' = Stimulation of ipsilateral afferent nerve, which inhibits the stretch reflex and the crossed extensor reflex alike, making no distinction between the "postural" and the "phasic" reflex. At n, slight after-fall of tension. As stretching force and contralateral afferent stimulation are continuing, tension redevelops. c' = Relaxation owing to cessation of contralateral stimulation. t' = Further relaxation to original position as stretching force is removed. Time in 0·1 second. Tendon movement multiplied 62 times. (Liddell and Sherrington, *Proc. Roy. Soc.*, 1924).

if while the quadriceps is under inhibition it is stretched, it gives the response characteristic of paralysed muscle (*v. inf.*). If an extensor muscle is contracting, a stretch applied to it further enhances its contraction to a considerable degree[1] (Fig. 22).

In the *spinal* animal stretch of the quadriceps gives a transient contraction —the "*knee jerk*"—which is a fractionated or abbreviated stretch reflex; in conformity with this view, it is found that pulling on the hamstrings inhibits the knee jerk (cf. p. 23). The stretch reflexes help to explain the mechanism of *stepping*. The flexor movement of the step stretches the extensor muscles; this does *not* arouse reflex contraction because they are reciprocally inhibited during this movement. At the completion of the flexion phase the concomitant inhibition ceases; the extensors find themselves in the stretched position, and being no longer inhibited actively contract

[1] It is also found that stretch of the quadriceps causes contraction of the opposite quadriceps (Phillipson's reflex): *e.g.* forced flexion of one leg at the knee causes extension of the opposite leg and foot (cf. p. 105).

and extend the limb. When the sole of the foot is pressed on the ground the "extensor thrust" reflex is set up, which produces a brief contraction of the extensors of the leg (cf. p. 105). As the knee is straightened, the quadriceps is no longer elongated; "the promoting stimulus is abrogated," and the stretch reflex ceases.

Properties of Posturing Muscle. — The decerebrate animal serves well for the study of the properties of muscle when it is concerned with postural activity only.

1. Normal movements are extravagant from the standpoint of expenditure of energy. Muscle maintaining posture has, in comparison, a *low metabolism*. The oxygen intake and CO_2 output of a decerebrate animal are about 25 per cent. higher than in an animal in which the chief motor nerves have been cut or in which all the muscles had been paralysed by curari.

2. Postural activity, unlike muscular movements, is relatively *unfatiguable*. A decerebrate animal has been kept standing for six days without showing signs of exhaustion. This is probably due to the fact that the fibres of the posturing muscle are not contracting continuously but in *rotation*. The maximum tension which the quadriceps (of the cat) will develop as a result of a tetanizing current is of the order of 30 kg.; the tension developed by this muscle during the stretch reflex is about 3–6 kg. According to the "all or none" law, individual muscle fibres always contract to their maximal extent or not at all; the lower tension obtained during the stretch reflex presumably means that only a small proportion of the fibres are contracting at one time. One can picture that the continuously acting stretching force stimulates different groups of receptors in turn, and thus reflexly activates in succession different parts of the quadriceps.

3. Posturing muscle tends to maintain any new position imposed upon it. To this property the term "*plasticity*" is applied. If the resistance of the knee extensors be overcome and the limb bent, it tends to remain in that position—"lengthening reaction"—(though it ultimately returns to its original position). If the leg is extended again, it tends to stay there—"shortening reaction"; whether the muscle fibres be lengthened or shortened they remain in the new position. Both these reactions are probably reflex in character. (*a*) To produce the *lengthening* reaction, a strong, *excessive* stretching force must be applied to the muscle; this excites muscle afferents which reflexly produce inhibition. Sherrington has demonstrated the presence of inhibitory afferents in the nerves to the quadriceps; if one of the four branches which supply the muscle is cut and the central end stimulated, the rest of the muscle is inhibited if it is in a state of activity. It thus appears that while slight stretch causes reflex contraction, violent stretch results in reflex relaxation. (*b*) In the case of the *shortening* reaction, when the knee is passively extended, the leg tends to droop by reason of its own weight; this sets up a stretch reflex (which possesses a very brief latency, 0·006 second), and immediately causes contraction of the muscle to maintain the new posture. The shortening reaction is grafted on to many reflexes. Thus if the crossed extensor reflex (p. 20) is produced in a de-afferented quadriceps recording isotonically, on cessation of the stimulus, the tension is maintained for a brief period (after discharge), and then rapid relaxation occurs; if the afferents from the muscle are intact, when the stimulus ceases, there is soon a slight decline from the maximum level; the tendency for the limb to fall

then causes reflexly a shortening reaction which results in the limb being maintained in its new position for a prolonged period (see Fig. 23).

4. The tension exerted by a muscle when carrying out movements depends on the initial length of the fibres. Up to a point the more the fibres are stretched, the greater the load which can be lifted. When muscle is acting posturally, the tension is more independent of the initial length of the fibres. This can be shown as follows: the leg of a decerebrate cat is allowed to project over the edge of a table. The knee is forcibly flexed, and weights are

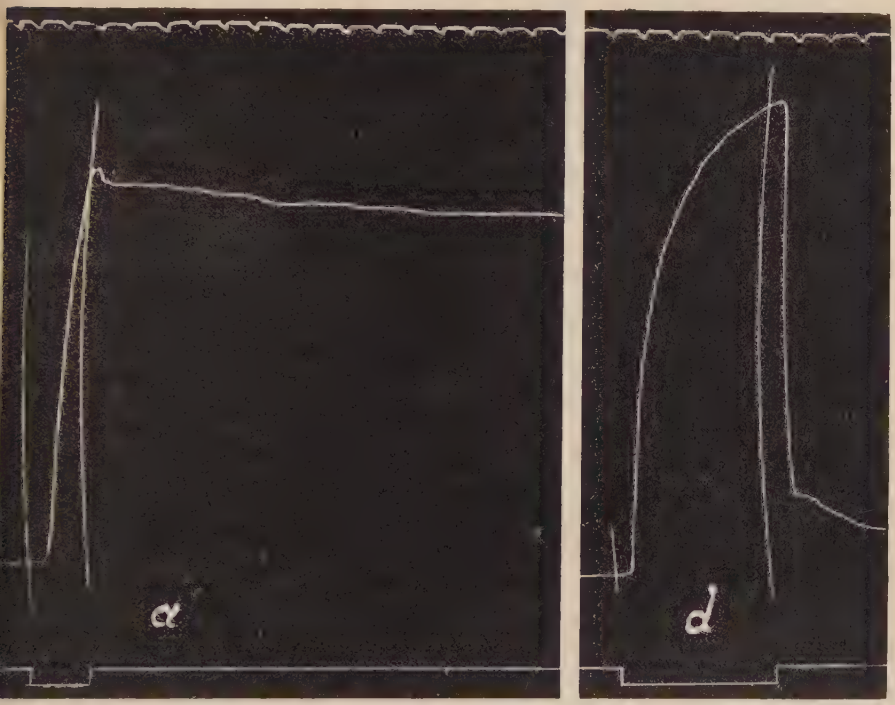

FIG. 23.—Crossed Extensor Reflex (isotonic) of Vastocrureus.

a Shows response of muscle with afferent roots intact; *d*, Same muscle with afferents cut 2 hours previously. Note that following "plateau" after-discharge there is in *a* slight decline and then there is appended a prolonged shortening reaction. (Sherrington, *Quart. Journ. Exp. Physiol.*, 1909.)

then hung on the ankle to determine the greatest weight which the quadriceps can support. Passively extend the knee again. Though the quadriceps fibres are now shorter, they can still maintain the same weight, *i.e.* exert the same tension.

Peripheral Mechanism of Posture.—In *vertebrate* skeletal muscle no example of a pure postural muscle can be recognized; the same muscle is used both for movement and for posture. It must be recognized that, in any complex movement, some groups of muscles are executing the movement, while others are chiefly maintaining posture. Thus in the scratch reflex of the

dog, three of the limbs, the head and neck are kept in a characteristic posture, while the fourth limb carries out the scratching.

Two kinds of fibres can be demonstrated in skeletal muscle : (1) *red* fibres, rich in sarcoplasm, with poorly marked transverse striations and nuclei scattered through the substance of the fibre ; the colour is due to the presence of a hæmoglobin derivative (myohæmatin) ; (2) *pale* fibres, with well-marked cross striation, scanty sarcoplasm, and nuclei limited to the under-surface of the sarcolemma. But it must be recognized that in addition numerous intermediate types of fibre can be found. In man, most of the muscles consist of mixtures of red and pale fibres ; though the red are said to predominate in some (*e.g.* soleus), and the pale in others (*e.g.* gastrocnemius). The red fibres are more primitive in structure ; they contract slowly after a longer latency, the duration of the contraction being three times that of the more quickly acting and more highly differentiated pale fibres. There are, however, no fundamental functional differences between them, and they have a similar innervation. There is *no* evidence in support of the view that the red fibres maintain tone and the pale fibres carry out movements.

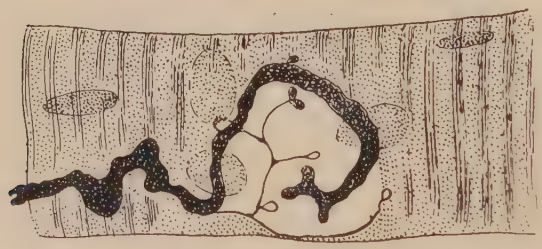

Fig. 24.—Skeletal Muscle Fibre supplied by both Myelinated (thick) and Non-Myelinated (thin) Nerve Fibres. —After Boeke.

Rôle of the Sympathetic. — 1. Histology. — Besides the motor end plates which are derived from medullated somatic nerves, there are undoubtedly non-medullated fibres passing to skeletal muscle. These have been proved conclusively to be derived from the sympathetic nervous system. In the cat, the anterior roots of the sixth to ninth dorsal nerves were severed, and the posterior root ganglia extirpated. Thirty days were allowed for degeneration, and then the intercostal muscles were examined histologically : no medullated fibres or sensory end organs could be detected, but the non-medullated fibres ending in their " terminaisons en grappe " were abundant and unaffected. These fibres must have arisen from peripherally situated ganglia—*i.e.* they were post-ganglionic sympathetic fibres (Boeke and de Barenne).

In the case of the eye muscles, practically every fibre shows sympathetic nerve endings ; these are less numerous in the limb muscles. It is important to note that the *same* muscle fibre may be supplied by both somatic and sympathetic fibres (Fig. 24).

2. Physiological Significance.—(*a*) It has been claimed that the sympathetic innervation is responsible for the maintenance of tone in skeletal muscle. It has been proved, however, that decerebrate rigidity is not abolished by section of the sympathetic nerves though later secondary changes may develop in the muscles owing to alterations in their blood-supply. Hunter and Royle claimed that section of the sympathetic supply to a limb which was spastic as the result of a pyramidal tract lesion (p. 76) causes marked

diminution of the hypertonus; but this has not been confirmed. There seems little doubt that muscle tone is a proprioceptive reflex controlled by the *somatic nervous system alone.*

(*b*) Orbeli recorded the contraction of frog's muscle in response to tetanic stimulation of the motor nerve repeated at short intervals. Fatigue gradually sets in, as shown by diminution in the height of the contraction. The sympathetic supply of the muscle was now stimulated (the motor stimulation was continued throughout the experiment); after a considerable latent period the size of the contractions became greater, and this effect persisted after sympathetic stimulation was discontinued (see Fig. 25). Stimulation of the sympathetic alone produces no recognizable effects on resting muscle. These experiments show that the sympathetic minimizes and delays the onset of fatigue in skeletal muscle, though its mode of action is undetermined.

(*c*) This conclusion is supported by the older work with *adrenaline,* which is sympatho-mimetic in it action (p. 127). If perfused muscle is excited until fatigued, the addition of small amounts of adrenaline to the perfusion fluid greatly increases the extent of the (diminished) contractions. In the

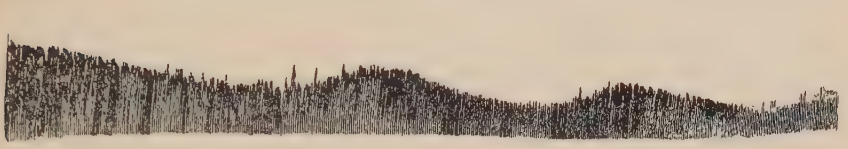

FIG. 25.—Effect of Sympathetic Stimulation on Skeletal Muscle of Frog.

A series of rapidly recurring twitches were produced by stimulating motor roots till signs of fatigue appeared. The sympathetic nerves were stimulated for the periods indicated by the signal above. After considerable latency, twitches increase, maximum effect occurring after cessation of sympathetic stimulation.—After ORBELI, *Pavlov Jubilee Volume,* 1924.

intact animal too, the injection of a dilute solution of adrenaline intravenously greatly increases for the next 5 to 20 minutes the force of contraction of fatigued muscle sometimes to a level *above* that obtained before the onset of fatigue. The excitability of unfatigued muscle to motor stimulation is also increased, and the height of contraction raised by the injection of adrenaline. This observation suggests that adrenaline does not act simply by neutralizing or destroying fatigue products.[1]

REGULATION OF POSTURE.—It is not yet possible to give an account of how the different levels of the brain and cord collaborate to regulate posture under varying conditions. Some light is thrown, however, on the rôle played by each part of the nervous system, by the study of animals (or men) in whom the neuraxis has been trans-sected at different levels.

"SPINAL" PREPARATION (cf. p. 102).—When the trans-section is through the mid-thoracic region, after the period of shock has passed off, postural activity returns slowly. Tone always remains considerably below normal; it is present mainly in the flexor groups, and so the limbs tend to adopt the flexed posture; the degree of contraction present is insufficient to support the weight of the body against the influence of gravity.

[1] Gruber, *Amer. Journ. Physiol.,* 1922, vol. lxi. p. 475.

"Decerebrate" Preparation (cf. p. 49 and Fig. 20).—Tone is present almost exclusively in the antigravity muscles (and is practically absent from the flexors); it is excessive in degree and is sufficient to maintain the animal in the standing position. If the eighth nerves and the proprioceptive impulses from the posterior neck muscles are intact, flexion or rotation of the head or alteration of the position of the head in space causes reflexly appropriate modifications in the posture of the limbs (cf. p. 61).

"Midbrain" and "Thalamic" Preparations (p. 62 and Fig. 20).—Tone is normal in distribution, is present in both extensor and flexor, and is sufficient to maintain the upright position. If the eighth nerves are intact the animal possesses the righting reflexes (p. 63) which enable it to regain the normal position if it is displaced from it. In *man*, however, lesions of the *pyramidal tracts* (p. 76) or of the *corpus striatum* (p. 80) without injury to the red nucleus, produce abnormalities of the tone, so that these systems are also concerned with the regulation of posture. It is probable, too, that the *cerebellum* controls the postural activity of the brain stem (p. 87).

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THE VESTIBULAR APPARATUS

Anatomy—Structure—Central connections—Extirpation—Mode of action—Relation of brain stem and vestibule to posture—"Standing" reflexes—"Righting" reflexes—"Stato-kinetic" reflexes—Barany's test.

The Vestibular Apparatus.—The vestibular apparatus plays a very important rôle in postural activity. It serves to adapt the position of the trunk and limbs to that of the head, and it supplies afferent impulses which enable the erect position of the head and the normal attitude of the body to be maintained.

Anatomy.—The term vestibular apparatus is used here to include the semicircular canals, the saccule, and the utricle. The membranous canals contain the endolymph and are enclosed in bony canals, from which they are separated by the perilymph. The semicircular canals are three in number: external or horizontal [lateral], superior, and posterior, each being in a different plane at right angles to the others. The left superior canal is in the same plane as the right posterior canal, and *vice versa*.

Each canal commences as a dilatation or ampulla. The canals open into the utricle by means of five apertures, one being common to the superior and posterior canals. The utricle communicates with the saccule by means of the ductus endolymphaticus. The canalis [ductus] reuniens unites the saccule and the duct of the cochlea.

Structure.—The canals are lined by three layers:

(*a*) An outer coat of loose fibrous tissue and blood vessels.

(*b*) A middle thick transparent layer forming a basement membrane.

(*c*) An inner layer of cubical nucleated cells.

In each ampulla is a projecting ridge called the crista. The corresponding projection in the saccule and utricle is termed the macula. The epithelium is tall and columnar, and surmounted by long, stiff, tapering hairs. Supporting these hair cells are thin fibre cells of Retzius. The hairs lie in a soft mucus-like material—the cupula terminalis. In the saccule and utricle small calcareous particles or otoliths are found in the mucus. Between the hair cells lie the fibrils of the eighth nerve. When the head is in the normal position, the macula of the utricle is approximately in the horizontal plane, with the otoliths lying on the macular epithelium ; the hairs of the hair cells project *upwards*. In the saccule, the macula lies in the vertical plane, with the otoliths on its outer side, and the hairs of the hair cells project horizontally outwards into the cupula. Magnus regards the otoliths as being attached to the macular epithelium by means of the mucus. When the otoliths are *pulling* on the epithelium, maximal stimulation is said to take place ; when they are resting on the epithelium, stimulation is at a minimum. Thus when the left side of the head is below, the otoliths of the left saccule are hanging down and in the position of greatest stimulation, but the otoliths of the right saccule are lying on the epithelium and are in the position of minimum stimulation.

Central Connections.—The fibres arising in the vestibule have a cell station locally in the ganglion of Scarpa [vestibular ganglion], and then pass as the vestibular division of the eighth nerve to the upper part of the medulla. The nerve enters the medulla ventral to the inferior peduncle and between it and the descending root of the fifth nerve, and terminates in the principal vestibular nucleus, and in a group of cells situated in the outer part of the floor of the fourth ventricle, the nucleus of Deiters [lateral vestibular nucleus]. From the vestibular nucleus axons pass to the cerebellum chiefly through the opposite inferior peduncle, but also through the inferior peduncle of the same side. From Deiters' nucleus axons pass to the middle line and bifurcate. The descending fibres pass into the antero-lateral region of the spinal cord as the *vestibulo-spinal* tract. The ascending fibres form the *posterior longitudinal bundle* [median longitudinal bundle] which can be traced through pons and midbrain. It lies in the floor of the aqueductus Sylvii, where it gives collaterals to all the oculo-motor nuclei and ends in the superior corpora quadrigemina. The vestibule establishes very important functional connections with the red nucleus [1] both directly and *via* the cerebellum and its superior peduncle (see pp. 63 and 86) ; fibres from the vestibular nucleus also enter the mesial fillet and pass to the thalamus and sensory cortex. The vestibule can thus (i) influence postural activity in the eyes, trunk, and limbs ; (ii) guide the cerebellum ; (iii) provide conscious information to the cerebrum.

Extirpation Experiments.—The effects are most serious in animals, such as birds, which carry out complicated and finely adjusted movements.

1. If both vestibules are destroyed, the animal cannot stand or fly or maintain any fixed position. It constantly moves about wildly, and a padded cage becomes necessary to prevent self-injury. There is tonelessness of the muscles, especially of the neck and trunk. The symptoms generally resemble those of cerebellar injuries. Gradually compensation is established chiefly through retinal impulses and cortical activity.

[1] The path taken by the fibres to the red nucleus has not yet been worked out.

2. Unilateral extirpation gives rise to complex derangements of postural activity.

(*a*) The *immediate* effects are skew deviation of the eyes, *i.e.* one eye rolls upwards and outwards and the other downwards and outwards ; nystagmus ; rotation and lateral flexion of the head to the side of the lesion ; spiral rotation of the trunk ; increase in tone of the extensor muscles of the normal side, and diminution of extensor tone on the side of the lesion. The skew deviation is minimal in the cat and the dog, and is only characteristic of animals with laterally placed eyes.

(*b*) The *permanent* effects are—

α. Nystagmus : there is a slow swaying movement towards the side of the lesion and a quick return towards the midline.

β. The reciprocal changes in tone and the head rotation persist.

γ. The rotation of the trunk diminishes (Magnus).

Probably the head rotation is due to the unantagonized action of the intact labyrinth. The abnormal position of the head secondarily alters the position of the body in a manner which will be explained below (see p. 61).

3. If one canal, *e.g.* the horizontal, is removed, spontaneous movements are set up in the plane of that canal, as no impulses are sent up to give information about the movement and thus check it.

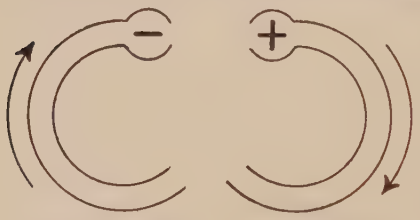

Fig. 26.—Diagram to illustrate Mode of Action of Semicircular Canals.

The arrow shows the direction of movement of the head. Owing to the inertia of the fluid the pressure in the left ampulla falls and in the right ampulla rises.

Mode of Action of the Labyrinth. — 1. Semicircular Canals.—The following experiment of Ewald makes clear how impulses are set up in the canals. Bore two holes in one bony canal. Stop the one farthest away from the ampulla with amalgam. Into the second hole introduce a rubber tube, down which air is gently blown. The membranous canal is thus compressed and the endolymph moves in the direction of the ampulla. Simultaneously the head and eyes are moved in the plane of the canal and in the direction of the current. The normal stimulus to the hair cells, therefore, is probably change of pressure in the ampulla.

To appreciate how the hair cells are stimulated naturally, it must be remembered that the endolymph possesses inertia and will not at once follow rotational movements of the head and the bony canals. From the diagram (Fig. 26) it is seen how, if the head is rotated from left to right, the lag in the endolymph causes a rise of pressure in the right ampulla and a fall of pressure in the left, and thus impulses pass up to the brain, of a complementary nature. As there are six canals arranged in all three planes, and the ampullæ of synergic canals (*i.e.* those in the same plane) are set facing one another, movements in any direction can be recognized.

2. Otolith Organ (Saccule and Utricle).—In the crayfish the otolith organ opens on to the surface. The otoliths can be removed and replaced by iron filings. If the position of the iron filings is altered by means of a powerful magnet, the crayfish correspondingly modifies the position of its body.

It thus appears that if the position of the head is altered, the otoliths stimulate a definite group of hair cells. The nervous impulses thus aroused give information as to the position of the head. The mode of action of the more complex otolith organ of the mammal was discussed on p. 59.

It must be clearly pointed out that the semicircular canals give information about *movements*, the otolith organ about the *position* of the head.

Relation of Brain Stem and Vestibule to Regulation of Posture.—The observations on the crayfish, the experiment of Ewald, and the results of extirpation clearly show that the vestibule normally plays an important part in the regulation of posture. The work of Magnus, Rademaker, and their co-workers has thrown further light on this subject and on the functions of the brain stem nuclei.

In the Decerebrate Animal: "Standing" or "Attitudinal" Reflexes.—The attitude of the decerebrate animal may be reflexly modified in complex ways (i) by alteration of the position of the head in space, and (ii) by changing the position of the head relative to the trunk. In the first case the afferent impulses arise solely from the vestibule ("tonic labyrinthine reflexes"[1]); in the second case additional afferent impulses come from the neck muscles ("tonic neck reflexes"[1]). The new position reflexly imposed on the body persists for as long as the new position of the head is maintained.

(i) Tonic Neck Reflexes.—To study these separately bilateral extirpation of the labyrinths is carried out. These reflexes are set up by *alterations of the position of the head relative to the body.*

(*a*) Ventroflex head: the fore limbs flex and the hind limbs become more extended.

(*b*) Dorsiflex head: the fore limbs extend and the hind limbs flex. The purpose of these responses is obvious: the position of the body is being adapted, *e.g.* "for looking under a shelf, or looking up to a shelf."

(*c*) Press ventralwards on the lower part of the cervical vertebral column: all four limbs flex ("*vertebra prominens reflex*"), as "in an animal crawling into a hole."

(*d*) Rotate or incline the head in various directions: to simplify description the limbs on the side to which the jaw is turned are called "jaw limbs"; the limbs to which the vertex is turned are called "skull limbs." In general it may be said that the "jaw limbs" extend (to support the weight of the head) and the "skull limbs" flex.

The centre for reflexes (*a*), (*b*), (*d*) is in C 1 and 2; the afferent impulses pass in the posterior roots of C 1–3 and are coming from the muscles of the back of the neck chiefly. The centre for (*c*) is in the lower cervical region.

(ii) Tonic Labyrinthine Reflexes.—These are studied after section of the posterior nerve roots of C 1, 2, 3 or after immobilizing the head, neck, and upper thorax by means of a plaster jacket (to prevent neck reflexes from coming into play). These reflexes are due to alterations in the position of the head relative to the horizontal plane.

(*a*) If the animal is placed in the *supine* position, maximum tone is present in the antigravity muscles. (*b*) In the *prone* position, with the snout 45° below the horizontal plane, tone in the extensor muscles is reduced to a minimum; in intervening positions intermediate grades of tone are present. The purpose of these reactions is not very clear; they disappear after section

[1] *i.e.* reflexes from labyrinth or neck which modify tone or posture.

of the eighth nerves and probably arise in the *otolith* organ. If an anæsthetized guinea-pig is centrifuged at high speed, the otolithic membranes are detached (as proved by microscopic examination) but the ampullæ of the semicircular canals are unharmed: the labyrinthine reactions are, however, no longer present. It appears that alteration in the position of the otoliths reflexly modifies tone in the muscles of the limbs. The *centre* for these reactions is in the neighbourhood of the vestibular nucleus.

As stated above (p. 60) after unilateral labyrinthine extirpation the unopposed activity of the intact otolith organ results in flexion and rotation of the head to the side of the lesion; this in turn evokes secondary modifications in the position of the limbs (neck reflex)—the "jaw limbs" extend and the "skull limbs" show diminished tone.

When tonic labyrinthine and neck reflexes are combined, they produce the algebraic sum of the separate responses. Thus, if the head is dorsiflexed in a decerebrate animal (with intact labyrinths), labyrinthine impulses produce increased tone in all four limbs and the proprioceptors from the neck tend to extend the fore limbs and flex the hind limbs. The actual result observed is extension of the fore limbs (both reflexes tend to increase extensor tone) and little change in the hind limbs (because the two reflexes are exerting antagonistic influences).

Fig. 27.—Posture of Limbs in Decerebrate Rigidity in Man, and the Effect upon them of Rotation of the Head.—Walshe (*Lancet*).

The attitudinal reflexes can be easily demonstrated in normal animals and man, where they are carried out more smoothly because the flexor muscles also participate in the reactions. A cat sees a piece of meat in the air: the head extends, the fore limbs extend, the hind limbs are unaffected, but can be suddenly extended when the animal wants to spring.

(iii) Walshe has shown in a case of decerebrate rigidity in man that complex modifications of tone follow alterations in the position of the head. If the head be rotated to the right, the right arm extends at the elbow and becomes abducted; the left arm becomes fully flexed with the hand touching the neck; the right leg is extended and the left leg is flexed (Fig. 27).

In the Thalamus and Midbrain Animal.—In the former the cerebrum has been removed and only the thalamus and brain stem are left; in the latter the thalamus has been removed too, but the midbrain is quite intact. On emerging from the anæsthetic such an animal first raises its head, then the fore part of its trunk, and finally assumes an easy standing position. It is seen that the position of the animal is a *normal* one (unlike the exaggerated standing posture of decerebrate rigidity); muscle tone is, therefore, normally dis-

tributed and is present in the flexors as well as in the antigravity muscles. Such a preparation is of course deprived of all volition, is a mere automaton and all its activities are reflex. The decerebrate animal keeps its head in whatever position it is put; these preparations possess the "*righting reflexes*," by means of which they are always able to bring their heads right way up, no matter what is done with them. The animal can be laid on its side or on its back, and it is found that the head at once rights itself, the body follows suit, and the animal resumes the upright posture.

The righting reflexes have been analysed as follows: if a thalamic animal, with both labyrinths extirpated, is held by its pelvis in the *air* in the supine or lateral position, the head and body remain in the new position and no attempt at righting is made.

(*a*) *Labyrinthine* righting reflexes: with the labyrinths intact, the pelvis may be placed in any position, or moved from one lateral position into the other, all the while the head is kept steadily in the normal upright position. By the method of "centrifuging" this can be proved to be due to an otolith organ reflex.

(*b*) *Body* righting reflexes: if the labyrinthless animal is placed on its side on a *table*, immediately the body touches the table the head is righted; this is due to asymmetric afferent impulses from the deep structures on the side of the body which is in contact with the table. If a weighted board is placed on the upper side of the animal so that identical impulses pass up from both sides of the body wall, the head falls back into the lateral position.

(*c*) These two reflexes, from the otolith organ and the body surface, act primarily on the *neck* muscles and right the head. The trunk, however, remains as before in the lateral position, so that the neck is twisted. This evokes a further reaction—"neck righting reflex"—which brings the thorax and lumbar region successively into the upright position. If righting of the head is prevented, impulses from the body surface may cause righting of the body directly.

The appropriate posture of the limbs is largely attained by impulses arising in the limb muscles themselves. Extirpation of the cerebellum has *no* effect whatever on any of the reflexes mentioned. The chief centre for these reactions, according to Rademaker, is the red nucleus. One very striking experiment of his may be mentioned. In a "thalamus" rabbit, a fine silk thread was introduced in the midline of the midbrain behind the decussation of Forel. Muscle tone was normal, and the righting reflexes were present. The thread was drawn forward. The animal at once fell, decerebrate rigidity developed, and the righting reflexes were lost. This experiment also emphasizes that the red nucleus is an important centre for the maintenance of the normal distribution of tone (in animals at any rate).

Optical Righting Reflexes.[1]—In the cat, dog, or monkey with both labyrinths extirpated, but with *intact cerebrum*, righting still occurs if the eyes are open, but not after blindfolding. The centre for the reflex is the *occipital cortex*, whence impulses pass to the neck muscles to right the head. In *man* the optic righting reflexes are much more important than the labyrinthine: thus an aviator passing through a cloudbank may emerge upside down, or he may fly in fog many miles wrong way up, in spite of intact labyrinths.

[1] These are absent in the rabbit.

Positive Supporting Reaction.—This is best seen in the intact animal after removal of the cerebellum. Press against the pads of the fingers or toes and dorsiflex the hand or the foot: the limb reflexly becomes stiff and can carry the body weight. The afferent impulses arise from the skin stimulated and from the muscles which are stretched. The reflex contraction is not limited, as in the myotatic reflexes (p. 52), to the muscles which are subjected to stretch, but involves the *antagonists too.* This is not so strange as may appear at first. The flexors are truly antagonistic to the extensors if, say, extension of a joint is desired; in the supporting reaction, *fixation* of the joints of the limb is aimed at, and this is best achieved by means of *simultaneous contraction* of flexors and extensors, which are thus co-operating best to attain the required end (cf. p. 66).

"STATO-KINETIC" REFLEXES.—The reflexes now to be dealt with are evoked by the initiation or cessation or variation of a movement and depend on stimulation of the semicircular canals.

i. *Rotation Reactions.*—If the subject is rotated on a turn-table, the head and eyes first turn in the *opposite* direction, in an attempt to fix the outside world, which appears to be "running away." If the rotation is continued, the inertia of the endolymph is overcome, and it takes up the movement of the head; if the eyes are closed, the head is kept still. If the rotation is suddenly stopped, the endolymph goes on moving because of its own momentum. If the rotation is to the right, the endolymph keeps on moving to the right. By consulting the diagram (Fig. 26), this will be seen to be equivalent to a head movement to the left. Conflicting sensations are thus coming from the vestibule and retinæ, and therefore giddiness is experienced. The subject gets the impression that he is moving involuntarily to the left, and to compensate he moves his head to the right

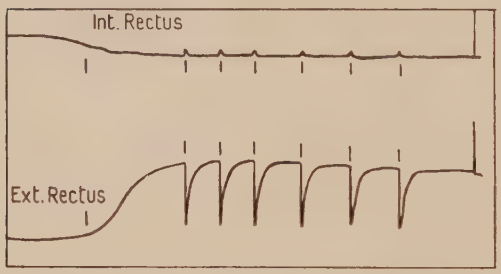

FIG. 28.—A Record demonstrating Reciprocal Innervation of Eye Muscles of Rabbit during Nystagmus set up by Irrigation of Ear.

Lower curve, external rectus; upper curve, internal rectus. Decerebellate preparation. —After DE KLEIJN.

Thus, on rotation to the right, the initial head movement is to the left; and on coming to rest, the movement is reversed.

Barany's test.—The semicircular canals in man can be readily stimulated. By throwing the head backwards 60° and looking to the opposite side at an angle of 50° from the middle line and up to the ceiling, the external horizontal canal is placed vertical. The right ear, for example, is then syringed with cold air, which causes (by convection currents) a downward movement of the endolymph; this is equivalent to moving the head to the opposite side (to the left). The patient complains of giddiness, and if allowed to stand will tend to fall to the right; nausea and vomiting may occur. The following results can be noted:

α. *Nystagmus.*—The short jerk is to the opposite side (the left), and the slow movement is to the same side (the right).

The slow deviation to the same side is due to impulses which reach the eye nuclei from the vestibule *via* Deiters' nucleus. The short jerk is a compensatory movement initiated by the cerebral cortex. The nystagmus illustrates well the law of reciprocal innervation (p. 22). De Kleijn removed the (right) eyeball in the rabbit and connected the internal and external rectus muscles to levers. Nystagmus was produced by syringing the (right) external meatus. The slow phase of the movement was to the right, and while the external rectus slowly contracted the internal rectus relaxed correspondingly slowly; in the quick phase the internal rectus contracted suddenly and the external rectus as rapidly relaxed (Fig. 28).

β. Past Pointing.—On attempting to raise and lower the arms and touch a given point on a tape (when the eyes are shut), the limbs deviate out to the stimulated side.

γ. *Spontaneous deviation* of the limbs occurs towards the stimulated side.[1]

ii. *Reactions to Movement in a Straight Line.*—(*a*) If the animal is suddenly lowered, the fore-limbs spread out so as to receive the weight of the falling body when the ground is reached. When a cat falls from a height it alights on its feet, as a result of a co-ordinated series of postural reflexes. Otolith righting reflexes bring the head right side up, tonic reflexes bring the trunk and limbs into their appropriate positions, and finally the "reaction to progressive movements" spreads the limbs out.

(*b*) On moving the animal vertically upward on a horizontal board, it sinks on flexing limbs. On ceasing the movement, the limbs extend.

The important part which the vestibule plays in regulating the posture of the body is very clear. It is surprising to find that extirpation of the cerebellum does not abolish any of the postural reactions which have been described above.

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VOLUNTARY MOVEMENT

Voluntary movement—Analysis of components—Agnosia—Apraxia—Structure of cortex—Anatomy—Stimulation—Jacksonian fits—Course of pyramidal fibres—Eye movements—Extirpation experiments—Emotional expression—Cortico-thalamo-mesencephalic path—Hemiplegia—Immediate and remote effects—Tone and reflexes—Clinical conditions.

Voluntary Movement.—The problem of voluntary movement is a much more difficult one than is usually suspected. It is customary to refer to any movement which is mediated by the pyramidal (cerebro-spinal) tract as "voluntary" in character. It must be remembered that we are not aware of the actual muscles involved in any movement; we simply notice the end result, which is displacement of joints or segments of the body in a certain direction and to a certain extent. Many of the component parts of a "voluntary" movement are entirely outside consciousness and have little of a voluntary character about them.

An attempt is often made to draw a distinction between "voluntary"

[1] It will be noted that the tendency to fall, the spontaneous deviation, the past pointing, and the slow phase of the nystagmus are all towards the syringed side.

and "automatic" movements, the movement of walking frequently being placed in the latter category. But no really hard-and-fast distinction should be made between these two types of movement. Walking has to be learnt by the child with difficulty, and at first requires constant attention. With the passage of the years and increased practice it becomes less "voluntary" and more "automatic" in character; so that movements of progression can proceed quite normally while we are thinking of something quite different. It would be preferable to grade movements as "less or more automatic" or "less or more voluntary," instead of attempting to distinguish two distinct hierarchies of movement.

The rôle of the pyramidal tracts in voluntary movement is often misinterpreted. They may be regarded as connecting links (analogous to the connector neurones of the involuntary nervous system (*q.v.*)), serving to unite the real centre for volitional action, which is probably situated in front of the motor cortex, with the lower centres in the pons, medulla, and spinal cord.

Probably all impulses for voluntary movement are transmitted by the pyramidal tracts. Voluntary movement may be completely lost in the human subject if both pyramidal tracts are destroyed. There is probably a perfectly distinct path from the frontal lobes to the pons for "involuntary" movements of emotional expression. It is thought that the corpus striatum in man has lost most of the motor functions it once had, and which it still carries out in the lower animals. This ganglion is probably not concerned at all with carrying out voluntary movements in man.

Many groups of muscles play a part in carrying out even quite a simple voluntary movement. We may recognize:

(*a*) Prime Movers or Agonists (Protagonists).—In such a movement as clenching the fist the agonists are the flexor muscles of the fingers and thumb.

(*b*) Antagonists.—In the above movement, the antagonists, or the muscles which would tend to interfere with the desired joint displacement, are the extensors of the fingers and thumb. In accordance with the law of reciprocal innervation, the antagonists are inhibited while the agonists contract, and thus facilitate the movement at the joint. It is not intended to convey the idea that the antagonists relax completely and immediately and always to the same extent when the agonists contract. The shortening of one group of muscles and the elongation of the opposing group just follow and keep pace with one another. Antagonists—contrary to what might be expected from their name—do their best to facilitate the wished-for movement, and so their behaviour is not stereotyped but varies under different conditions. (1) In ordinary displacement of a joint they harmoniously relax to permit the movement to take place.[1] (2) In violent contraction of the agonists against resistance, the antagonists relax very quickly and completely. Thus when the arm is raised above the horizontal on to a high shelf, the deltoid as agonist will contract. A strong downward movement of the extended arm is now made against the resistance of the shelf. The deltoid which normally raises the arm is now the antagonist. Though no movement of the arm occurs, the deltoid is felt to become lax, *i.e.* it has been reciprocally inhibited. (3) Sometimes the antagonists may co-operate with the agonists by actually contracting too, as in the straight left of the boxer, in which agonists and antagonists are both simultaneously contracted to keep the joint unmoved.[2]

[1] Cf. Fig. 11, p. 24. [2] Cf. also "Positive Supporting Reaction," p. 64.

It may be repeated that the antagonists will always act in the most perfect functional harmony with the agonists to attain the end in view. By applying suitable tambours to the muscles and connecting with recording levers, a graphic representation of the behaviour of the different components of the movement may be obtained.

(*c*) Synergic or Fixing Muscles (Synergists).—In clenching the fist, the synergic muscles are the extensors of the wrist which greatly facilitate the precise movement. Any one can readily demonstrate for himself that when the fist is normally clenched the wrist becomes dorsiflexed and that this movement becomes uncomfortable if the wrist is held quite horizontal. In very firm closure of the fist, the triceps contracts too and acts as a synergist, by preventing other joints being moved (in this case the elbow-joint) apart from those actually engaged in the desired movement.

It is desirable to note here certain groups of muscles that are normally associated together in carrying out voluntary movements (Wilson):

I. Head, Face and Neck.—(1) Shut eyes: eyeballs roll up.

(2) Turn eyes to side: head turns also.

(3) Open mouth against resistance: head extends.

(4) Turn eyes up: forehead wrinkles, head extends.

(5) In supine position: flex head on chest, recti abdominis contract.

II. Arm.—(1) Abduct extended arm at shoulder: opposite erector spinæ contracts.

(2) Open closed hand: flexors of wrist contract, extensors of wrist relax.

(3) Abduct little finger: abductor ossis metacarpi pollicis contracts.

III. Trunk and Legs.—(1) Supine position: lift up one extended leg (*i.e.* flex limb at hip): contralateral hamstrings contract.

(2) Erect position: abduct one extended leg at hip: opposite tensor fasciæ femoris contracts.

(*d*) Movements of Co-operation (Wilson).—These may be defined as movements which precede or accompany the prime movement and make it easier to carry out. This conception is best illustrated by examples:

(1) Order a person sitting in a chair to stand up. The essential movement is to rise from the chair. Before that is attempted, however, he brings his feet in underneath the body to a point almost under his centre of gravity; this in normal people forms an essential preliminary to rising. Again, a hand is often stretched out to grasp the side of the chair to help the body up. These movements of co-operation have often been referred to as "associated movements." This latter term is an undesirable one, and is best reserved for certain reflex movements which can be elicited on the paralysed side from the sound side in cases of unilateral pyramidal injuries (hemiplegia) (p. 76).

(2) Attempt to turn round in the chair with the hands folded on the chest. If the movement is to the right, the subject first abducts his right leg; as this "auxiliary" movement is closing, he carries out the prime movement of turning the body. As this is being completed, he adducts the left leg up to its fellow.

(3) Arm-swinging in walking is a movement of co-operation helping to maintain the balance of the body. It can be voluntarily dispensed with, and one can walk with the arms behind the back, but there is consciousness of a sense of lack of ease. An athlete uses this movement of arm-swinging in a powerful manner to help propel himself along.

It is clear that a "volitional" movement involves the agonists, the co-ordinated action of the antagonists, the assistance of the synergists to fix certain joints, and the help of various extraneous groups of muscles to carry out movements preceding or accompanying the prime movement in order to make the latter as easy and effective as possible.

In addition, however, the component parts of the movement must follow one another in appropriate sequence, and the whole movement must be correctly related to the stimuli which aroused it.

The sensory cortex does not merely receive visual, auditory, tactile, and other sensations, but such information is correlated and associated with memories of sensations previously received (p. 44). In this way we recognize the nature of objects and their uses. Stored in the parietal lobe, too, are memories of the various movement patterns we have carried out, and these memories are probably revived before a voluntary movement is repeated. We all know the difficulty with which even apparently simple movements are carried out for the first time, and how they become progressively simpler with repetition.

Before we can carry out volitional movements we must first have a clear "*general idea*" of the action; we must know what is the objective we wish to attain. The analogy of the control of an army may be of some help. An army must have a proper intelligence service (=sensory tracts and sensory cortex) and proper records must be kept. The staff must have some knowledge and experience of military tactics (=*memories of movements*). The general plan of campaign must be thought out on the basis of this information and knowledge (="*general idea*" of action). Sound staff work must be done to devise how best this general plan can be translated into action, *i.e.* the "general idea" of the movement must be analysed into its component parts. The sequence of the movements, their interrelations, their duration and intensity must all be arranged. Lastly, in the case of the army, appropriate and detailed messages must be sent to officers commanding the various units. In the case of the body, similar detailed instructions must be sent to the motor cortex and thus to the skeletal muscles.

We can now see in how many ways voluntary movement can be interfered with by defective function of other regions of the cortex than the so-called "motor cortex." Following Kinnier Wilson, we may make the following classification:

1. If the nature of the object is not recognized—the condition called "*agnosia*" is present (see p. 47). A man shown a pencil may not recognize it as such, but think it is a cigar and use it accordingly. The movement is planned and executed correctly, but the effect is ludicrous because the idea in the patient's mind of the nature of the object was incorrect.

2. The nature of the object may be recognized, but as a result of want of attention, or deficient retentiveness of memory, the main idea of the movement may not be analysed into its component parts. "*Intrapsychical function*" is disturbed. A man was supplied with a cigar and matchbox, both of which he recognized. When asked to use them, he opened the matchbox and stuck the cigar in and tried to shut the box as though it were a cigar-cutter. Then taking the cigar out, he rubbed it on the side of the box as though it were a match. The main idea of the action was to light

the cigar, but the components of the idea were not directed to the proper object nor followed in the right order.

3. Lastly, the nature of the object may be recognized, the general idea of action and the staff work are normal, but the messages do not reach the motor cortex intact—a normally worked-out idea is not exteriorized into the corresponding pattern of movements. Such a condition is termed *motor apraxia*. The nature of the disturbance is best illustrated by quoting Liepmann's classical case. The case was one of right-sided motor apraxia, the left side being normal. There was no paralysis on the right side. When asked to brush the examiner's coat, he took the lower corner of the coat correctly with the left hand and held it ; but with the right hand he picked up the brush and made a rhythmical series of movements in the air above his right ear. At the telephone, he put the receiver to his ear with the left hand, but with the right hand he took the mouthpiece and put it to his forehead, making nodding and puffing movements all the while. Then he said, " Je comprends bien ce que vous voulez, mais je ne parviens pas à le faire."

Localization.—It is believed that the general idea of the action is devised on the left side of the cortex, and what we have called the " detailed staff messages " pass from the *left frontal lobe* to the motor cortex of *both* sides of the brain. The left motor cortex is reached by short connecting fibres, while the fibres for the control of the right motor cortex must pass through the corpus callosum. Motor apraxia has been found following lesions of the left frontal cortex or subcortex and of the corpus callosum.

Structure of the Cortex.—Bolton describes five layers, which vary in their relative development in different regions of the cortex. From without inwards the layers are : (1) Outer fibre ; (2) outer cell ; (3) middle cell ; (4) inner fibre ; (5) inner cell.[1]

1. The outer fibre layer consists chiefly of a thin stratum of fibres running parallel to the surface of the brain [depth=0·277 mm.].

2. The outer cell layer is made up of pyramidal-shaped cells which increase in size from without inwards. It is the last layer to appear in the fœtus and develops slowly after birth, till it forms over half the depth of the cortical grey matter [0·836 mm.]. Numerous transversely running fibres are found in this region, forming the " outer line of Baillarger."

3. The middle cell layer consists of small stellate cells, and is most developed in the visual cortex. Here the layer is divided into two parts by the transverse line of Gennari [0·241 mm.].

4. The inner fibre layer forms the inner line of Baillarger. In the motor cortex, however, numerous large pyramidal-shaped cells appear, arranged in clumps or cell nests of Betz. These cells give rise to the pyramidal tracts [0·236 mm.].

5. The inner cell layer consists of scattered cells which are irregular in size and shape, the so-called polymorphous cells. The layer is well marked in the island of Reil and the hippocampal region [0·302 mm.].

The Motor Cortex.—The motor area occupies the whole length of the precentral convolution, and in most places the whole or greater part of its width. It extends backwards into the floor and posterior wall of the fissure

[1] A very detailed account of the histology of the different regions of the cortex is given by von Economo, *Zellaufbau der Grosshirnrinde des Menschen* (Berlin, 1927).

of Rolando [sulcus centralis], but never extends over on to the post-central convolution. At its upper edge it extends down on to the mesial surface of the hemisphere. Its anterior limit is not coincident with any fissure, and it may involve and even cross the superior and inferior precentral fissures. The genua form a reliable guide to the position of the different functional areas. The upper genu in the chimpanzee is at the junction of the arm and leg areas, and the lower genu at the junction of the arm and face areas. In the orang the face area is larger, and a third genu is present at the junction of lip and tongue areas.

Stimulation of the Cortex.—Electrical stimulation of the motor area results in movements on the opposite side of the body. It is very important to remember that the movements are always co-ordinated in character. One group of muscles (the agonists) are found to contract, and the opposing group (the antagonists) will simultaneously relax. In other words, the law of "reciprocal innervation" holds good for the motor cortex.

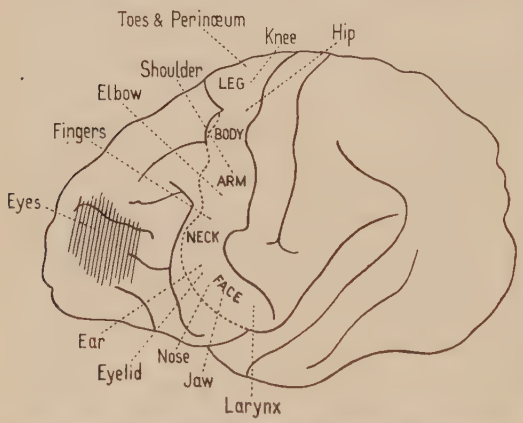

FIG. 29.—Diagram of Outer Surface of Cerebral Cortex to show the Arrangement of the "Motor Centres."—After SHERRINGTON.

The order of the centres can be mapped out, and is found to be, from below upwards: larynx, tongue, jaw, mouth, nose, ear, eyelid, neck, hand, wrist, elbow, shoulder, chest, abdomen, hip, knee, ankle, toes, perineal muscles.

There are several points to notice in this connection. (1) "The man is represented upside down." (2) When the terms, tongue, jaw, hand are used in the list, we are not referring to muscles but to definite movements, such as opening or closing of the jaw, flexion or extension of the fingers. (3) In the head, the order is larynx, the inside of the mouth (tongue), then the muscles round the mouth (jaw, etc.), and highest, the more distant structures (ear, eyelid). (4) The hand is the part of the arm which follows immediately on the face, and this may perhaps be remembered by considering the close relation of the hand to the face in the taking of food. (5) The hip follows immediately on the abdomen. (6) The toes and the perineum are associated together on the highest part of the convolution, and on the inner surface of the hemisphere.

"Jacksonian Fits."—It is doubtful if mechanical stimulation of the human cortex is adequate to excite a response. As a result of affections of the cranial bones (*e.g.* depressed fracture), or of the meninges (hæmorrhage, inflammation), or of the cortical tissue itself, local anæmia of a small area of the motor cortex may be produced, which serves as an effective stimulus. The corresponding part of the body first becomes tonically contracted and

then clonic jerkings occur. The movement may involve other parts if the stimulus involves adjacent areas of the motor cortex. Thus a fit beginning in the elbow will spread *via* shoulder, to trunk, hip, knee, and toes, and *via* the wrist to fingers, neck, and face. These fits of local onset are called "Jacksonian fits." The patient may remain conscious throughout the fit, but if the opposite cortical area is affected, consciousness is usually lost.

Course of the Pyramidal [Cerebro-spinal] Tracts.—The pyramidal fibres converge from the cortex through the corona radiata to reach the *internal capsule*. This is a path of white fibres lying between the basal ganglia, limited externally by the lenticular nucleus, and internally by the caudate nucleus and optic thalamus. In horizontal section it is **V**-shaped, the point of the **V** looking inwards. The pyramidal tracts lie in the bend (the genu), and the anterior two-thirds of the posterior limb [occipital part]. The order of the fibres from before backwards is now eyes, head, mouth, tongue, shoulder, elbow, wrists, fingers, trunk, hip, knee, toes. Some re-arrangement has taken place in the fibres from the arm, and it is the shoulder (and not the fingers) which follows on the face. Immediately behind the pyramidal tracts lies the condensed sensory path, and the visual path a little farther back. More posteriorly still lie the auditory fibres and the temporo-pontine tract. In the anterior limb [frontal part] are found fibres from the frontal lobes to the midbrain (eye nuclei) and pons. Obviously a small injury in this region can produce the most widespread motor and sensory disturbance.

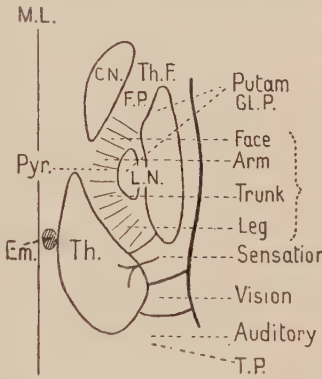

FIG. 30.—Horizontal Section through the Base of the Brain to show the Basal Ganglia and the Internal Capsule (Diagrammatic).

M.L. = Middle line; Pyr. = Pyramidal tract; Em. = Path for emotional expression; C.N. = Caudate nucleus; Th. = Optic thalamus; Th.F. = Thalamo-frontal; F.P. = Fronto-pontine; Putam. = Putamen; Gl.P. = Globus pallidus; L.N. = Lenticular nucleus; T.P. = Temporo-pontine.

In the *crus* the fibres lie in front of the substantia nigra, occupying the middle three-fifths of this region. The inner fifth carries the fronto-pontine and the outer fifth the temporo-pontine fibres. In the *pons*, the fibres are broken up into a series of scattered bundles by the nuclei pontis and the crossing fibres of the middle peduncle, which connect up the pons with the opposite lateral hemisphere of the cerebellum. In the *medulla* the fibres reunite once more to form a compact mass projecting anteriorly. In the lower part of the medulla, the decussation takes place. Most of the fibres cross over to the opposite side and backwards, to come to lie in the lateral columns of the spinal cord as the crossed pyramidal [lateral cerebro-spinal] tract. Some stay on their own side and in their original position, and continue into the cord next to the anterior median fissure as the direct pyramidal [anterior cerebro-spinal] tract. The crossed fibres end, not round anterior horn cells as one would naturally expect, but round posterior horn cells at different levels at the cord, the impulses presumably being relayed on to the anterior horn cells. The reason for this is not clear; it may allow

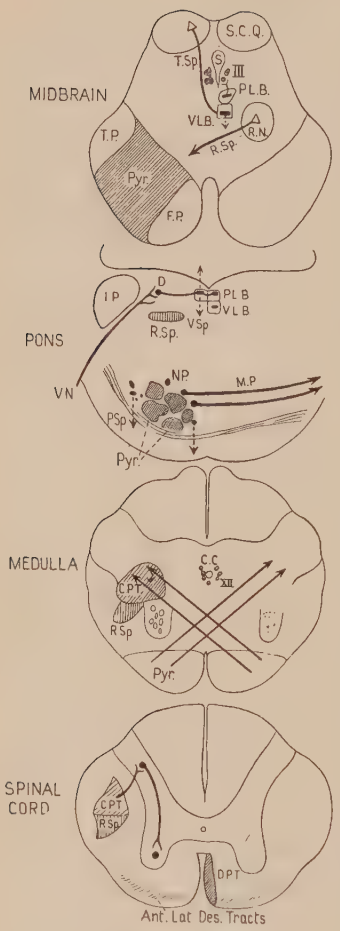

FIG. 31.—Diagram of Motor Tracts.

S.C.Q. = Superior corpora quadrigemina; T.Sp. = Tecto-spinal tract which passes down in V.L.B. = Ventral longitudinal bundle; S. = Aqueductus Sylvii; P.L.B. = Posterior longitudinal bundle; III. = Nucleus of third nerve; R.N. = Red nucleus; R.Sp. = Rubro-spinal tract; Pyr. = Pyramidal tract; T.P., F.P. = Temporo-pontine, fronto-pontine fibres; I.P. = Inferior peduncle of cerebellum; V.N. = Vestibular nerve; V.Sp. = Vestibulo-spinal tract; D. = Deiters' nucleus; P.Sp. = Ponto-spinal tract; N.P. = Nuclei pontis; M.P. = Middle peduncle of cerebellum; C.C. = Central canal of spinal cord; C.P.T. = Crossed pyramidal tract; D.P.T. = Direct pyramidal tract; Ant-lat. Des. Tracts = Antero-lateral descending tracts.

for some rearrangement of the impulses in the cord. The direct pyramidal fibres are of no practical importance. They do not extend as a rule beyond the lower cervical or mid-dorsal region. They cross in the anterior white commissure, to end round posterior horn cells of the opposite side.

Besides the main pyramidal decussation, fibres have been constantly crossing in the brain stem to reach the motor *cranial* nuclei of the opposite side. The connection here, too, is not a direct one, but through the large sensory masses, such as the substantia nigra. Collaterals are also given to the *nuclei pontis*, and connection is thus established with the opposite lobe of the cerebellum

The Betz cells and their axons, the pyramidal tracts, are usually referred to as the *upper motor neurone*. The anterior horn cells and their efferent fibres constitute the *lower motor neurone*.

Myelination. — Flechsig has laid it down that no tract functions until all the fibres composing it have myelinated to their terminations. The pyramidal tracts at birth have only myelinated as far as the decussation in the medulla, and the medullary sheaths are not completely developed till the second year of life.

It is clear that, if Flechsig's law holds good, such movements as are carried out by an infant are controlled by other paths than the pyramidal tracts. Many of the apparently voluntary movements of a baby may be reflex in origin; emotional expression is thought to be carried out by a tract which arises in the cortex, but which is quite independent of the pyramidal tracts (cf. p. 74).

Eye Movements.—In the middle and inferior frontal convolutions is an area which probably controls all movements of the eyeballs; but stimulation of this region, curiously enough, only gives rise to lateral movements, *i.e. conjugate deviation* of both eyeballs to the opposite side. The "eye centre" is not continuous with the general motor area, but is separated from it by

a definite strip of inexcitable grey matter. Stimulation of the tip of the occipital lobes gives similar results. Stimulation of the left cortex thus produces movement of both eyes to the right. These fibres for conjugate deviation are believed to cross in the midbrain and end chiefly round the sixth cranial nucleus (but also round the third and fourth nuclei). Each sixth nucleus innervates the external rectus muscle of its own side and also the internal rectus of the opposite side. This statement must not produce confusion. The internal rectus is supplied by the third *nerve*, but the fibres have had their origin in the opposite sixth nucleus, and simply use the third nerve as a convenient vehicle.

With these facts in mind we can consider Sherrington's beautiful demonstration of reciprocal innervation of the eye muscles. In the monkey, if all the nerves supplying the muscles of the eye are cut, the tension of the connections of the eyeball keeps the globes parallel, and if the eye is rotated away from the central position, considerable resistance is felt. Cut the third and fourth nerves of the left eye. The only nerve left intact is the sixth, and naturally the eye rotates outwards from the unopposed action of the external rectus. Expose the frontal lobes on the left side, *i.e.* on the same side as the eye operated on. The left frontal lobe, as we have seen, produces contraction of the right external rectus and of the left internal rectus. In the left eye the internal rectus cannot contract, because the nerve carrying its motor fibres (third) has been cut. It is obvious that the internal and external recti are antagonistic muscles, and that if one were stimulated the other should be inhibited. In the case of the left eye, as the motor cells supplying the internal rectus are stimulated from the cortex, the cells innervating the external rectus should be inhibited. This is exactly what happens. The external rectus relaxes, and the left eye moves to the middle line.

It follows that in *irritation* of the frontal cortex, there is movement of both eyes to the opposite side (" conjugate deviation " away from the side of the lesion). If the cortical centre for eye movements is destroyed on one side, the opposite centre acts without opposition, and so both eyes deviate *towards* the affected side.

As each sixth nerve nucleus causes movement of both eyes to its own side, irritant lesions of the sixth nucleus will cause conjugate deviation towards the side of the lesion ; while destruction of one sixth nucleus leaves the opposite nucleus unopposed, and so it will cause both eyes to deviate away from the side of the lesion.

Extirpation Experiments.—(*a*) It must be borne in mind that it is unsafe to argue too closely from experiments carried out on the lower animals, for man is much more dependent than they are on the pyramidal tracts. In the monkey the motor cortex on both sides may be completely extirpated and paralysis of the body results. This paralysis is by no means permanent, for it passes off in about six weeks. The monkey then appears able to carry out its customary movements in a fairly normal manner. It is not possible to say for certain how this compensation is established. A " thalamic animal," as is well known, can carry out reflexly movements of great complexity if appropriate stimuli are applied (cf. p. 62).

(*b*) To study the functions of the pyramidal tracts in *man* it is necessary to consider the findings in a case in which the pyramidal tracts on the two sides have been destroyed ; this results in paralysis of the two halves of the

body—a condition called "double hemiplegia." Voluntary movement is then found to be completely abolished. Thus one patient lost all voluntary movement in the facial muscles; biting, swallowing, elevation of the palate, and laryngeal movements were abolished; nor could the respiratory muscles be voluntarily influenced. Rhythmic respiration proceeded, but forced inspiration or expiration or voluntary coughing was lost. It was noted in this case that in marked contrast to the complete loss of voluntary movement, emotional expression remained intact, and, in fact, was exaggerated in extent. The patient laughed continuously and uproariously at the slightest provocation. It will be convenient to consider briefly at this point the mechanism of emotional expression.

Emotional Expression.—In expressing the emotions of joy and sorrow, complex movements of the somatic muscles occur and certain visceral changes take place. The muscles chiefly employed are the facial and the respiratory.

Laughter.—The facial movements need no description. Rhythmic breathing is interrupted by a prolonged inspiration followed by a series of short and broken expirations. The laughter sounds are of laryngeal origin and vary in character and pitch. If the laughter is overwhelming, other muscles are involved; movement is diffused over many muscle groups, and the subject may even roll on the floor.

The visceral changes include increased glandular secretion, and relaxation of the arterioles and capillaries. The skin reddens and glows, and the eyes sparkle.

Crying.—The facial expression is the reverse of that of joy. The respiratory movement consists of short interrupted inspirations and occasional prolonged expirations. Apart from the facial and respiratory movements, there is inhibition of the rest of the body musculature. There is general lassitude, pallor, cold skin, and sunken features.

Subjective emotional feeling seems to depend on the associated visceral manifestations, and not on the somatic movements. There may be complete paralysis of the facio-respiratory muscles for emotional movements, and yet joy and sorrow are felt acutely.

If the pyramidal tracts are destroyed on one side, voluntary movements are lost on the opposite side (hemiplegia). Emotional expression, however, persists on the affected side.

Even in cases of double hemiplegia, in which *both* pyramidal tracts are destroyed, emotional expression persists in an exaggerated form. This seems to show clearly that the pyramidal tracts do not initiate this type of movement, rather the reverse—they tend to inhibit it. We can, of course, voluntarily simulate to some extent the facio-respiratory movements of laughing and crying. As a rule, however, these complex movements are carried out involuntarily; with the proviso that we have some power of *checking* emotional expression. Laughter may be stifled and tears restrained to a degree which varies with different races and different individuals according to custom and practice. Lesions of the pyramidal tracts *release* the facio-respiratory mechanism from this inhibitory cortical control, and so emotional expression tends to be abnormal and unchecked.

Arising from the under surface of the frontal lobes (and perhaps the parietal lobes too) is a tract which passes towards the midline. It skirts the inner surface of the optic thalamus (without actually passing through it) and lies close to the third ventricle. The tract continues through the midbrain

into the pons and medulla, lying in the tegmentum near the middle line (Spencer). There is some experimental and clinical evidence that this tract is responsible for emotional expression.

1. In the chimpanzee, tickling produces a " smile " with retraction of the lips. The breathing becomes more rapid and vocal, and we are assured that a sound like Ha ! ha ! can be heard whispered. Identical facio-respiratory movements can be elicited if the cut surface of the midbrain is stimulated near the midline to the inner side of the red nucleus. In other words, laughter sounds and expression can be produced by stimulating the tract just described (Graham-Brown).

2. Cases are on record in which voluntary movement was retained but true emotional palsy was present. The lesions were found in the midbrain region damaging the path described, and *not* affecting the pyramidal tracts at all.

We may conclude there is a separate *cortico-thalamo-mesencephalic path* to the facio-respiratory nuclei which can produce laughing or crying. Emotional expression is as a rule " involuntary," and is only partially under pyramidal *inhibitory* control. In double hemiplegia, disseminated sclerosis, cerebral vascular degeneration, spastic bulbar paralysis—in fact, any condition with extensive bilateral pyramidal injuries—we may expect emotional overaction at the slightest provocation, without the patient in the least feeling subjectively the emotion he is so emphatically exteriorizing. The patient sheds tears or laughs when feeling no emotion whatever. In unilateral pyramidal lesions, emotional expression is retained.

Unilateral Lesions of the Pyramidal Tract in Man.—We will describe the effects of an acute lesion of the pyramidal tracts where they lie condensed in a small area in the internal capsule, as when the blood vessels supplying this region become suddenly thrombosed. In suitable cases the effects on movement and reflex function can be studied without any complicating general systemic disturbance.

1. All the symptoms are present on the opposite side of the body.[1] It may be laid down as a general law that if any great catastrophe occurs in the central nervous system, function is disturbed even in regions remote from the structures affected. So we find that the muscles of the opposite side are flaccid and toneless, and their deep reflexes are lost, though these depend on brain-stem and spinal-cord reflex arcs. It is customary to state that all the muscles on the opposite side of the body are paralysed. This, however, is not strictly true. Certain regions are scarcely affected at all, *e.g.* the muscles of the eye, the chest, trunk, and abdomen. In other words, the paralysis only involves the opposite arm, leg, and face, and is flaccid in character. Muscles usually acting bilaterally tend to escape, possibly because the nuclei are united by commissural fibres, or because the pyramidal tract of one side directly controls the nuclei of both sides in the case of these muscles. Eye movements are preserved, because there is a distinct path from the frontal lobes to control them (p. 72).

2. When recovery from the initial state of shock occurs, power returns to the arm and leg, and finally the subject may get about with little more disability than a slight limp. This has been claimed as proving that " crude voluntary movements " are carried out by the non-pyramidal paths presided over by the corpus striatum. More accurate study of the physiology of the

[1] Paralysis of one half of the body is called " hemiplegia."

corpus striatum does not support this view. The return of some power may be due to recovery of a few pyramidal fibres which were compressed but not totally destroyed by the initial lesion. Finer voluntary movements, such as those carried out by the hand, tend to be permanently lost or impaired.

Emotional movement is retained on the affected side, for, as explained (p. 74), a separate path is responsible for this kind of movement.

Certain "*associated*" movements can be reflexly aroused on the affected side from the sound side. If the normal hand is clenched, a similar movement occurs on the paralysed side. On trying to rise from the bed with folded arms and legs apart, the affected leg flexes on the trunk, but not the healthy one. These reflex movements are probably due to the released activity of certain lower centres.

Tone.—It is usually stated that tone is increased and that a condition of hypertonus or *spasticity* is present. We have defined muscle tone as being concerned with maintaining positions or postures. By noticing the position of the limbs we can determine whether tone is normal in distribution or not. The upper limb, instead of lying by the side in the customary way, is adducted at the shoulder, the elbow is semi-flexed, the forearm is pronated, and the wrist and fingers are flexed. This position is maintained indefinitely without fatigue, and is not voluntary in character. It is also difficult to move the limb into any other position. The limb is placed and fixed in this unnatural posture. The term spasticity refers chiefly to the factor of fixation. The leg is extended at the knee and physiologically extended at the ankle—which means anatomical plantar flexion. In the condition of decerebrate rigidity in man (p. 51), the arm and leg are in exactly the same condition. As the higher centres have been cut off, certain centres in the brain stem, chiefly Deiters' nucleus, are "released" to function as they wish, and they reflexly maintain the limbs in this position. The muscles do not waste greatly, because though not used in voluntary movement they are continuously in action to maintain the posture described; the electrical responses are normal. Lesions of the posterior nerve roots abolish the spasticity and the muscles become flaccid.

If one attempts to flex the knee, great resistance is met, presumably because the stretching force applied to the quadriceps elicits a reflex contraction (cf. p. 52); if great force is applied, the quadriceps suddenly relaxes, and the knee rapidly passes into the flexed position—this seems analogous to the "lengthening reaction" which is set up by excessive stretch which stimulates the self-inhibiting afferents in the muscle (cf. p. 54).

The state of the *deep reflexes*, such as the knee-jerk or the ankle-jerk, usually runs parallel with the degree of tone in the muscles involved. In the lower limb the tone of the quadriceps and the posterior calf muscles is increased, and so we find the deep reflexes appertaining to them are brisk in character and tend to be sustained.

Ankle clonus is also due to the state of heightened muscle tone. If the ankle is forcibly dorsiflexed, rhythmic movements of dorsiflexion and plantar flexion at the ankle-joint take place. Owing to the increased tone of the posterior calf muscles, stretching of the fibres sets up not a simple reflex contraction or ankle-jerk, but a rhythmic series of contractions or clonus.

Superficial Reflexes.—The exact arc of the superficial reflexes is not known. The efferent limb of the arc may be the pyramidal tracts, for when

they are destroyed these reflexes can no longer be obtained. The superficial reflexes commonly tested for are :

1. Abdominal : stroking the skin of the abdomen produces contraction of the underlying muscle.

2. Cremasteric : stroking the inner side of the thigh results in the testis being retracted towards the inguinal canal.

3. Plantar : stroking the sole of the foot produces a downward movement (plantar flexion) of the great toe and the small toes.

As stated, all the superficial reflexes are *lost* in hemiplegia on the affected side.

From the sole of the foot, however, a reflex can be elicited, different in every respect from the usual plantar response. The kind of stimulus which is now employed must be nocuous or painful, such as firm scratching with the finger-nail. The reflex can be elicited from a fairly wide area, from the calf, the thigh, and even as high as the groin ; it consists first of an upward movement of the great toe and fanning out of the small toes. It may spread and produce upward movement (dorsiflexion) of the ankle, flexion of the knee, and even flexion of the hip. If this response be compared with the " flexor " or withdrawal reflex of the spinal animal (p. 102), it is found to be identical with it in every respect. Clinically, the whole reflex described is not usually obtained. The movement is limited to the great toe and small toes, and is called *Babinski's sign.* Reference must be made to some confusion that exists in the nomenclature. This reflex is often called the " extensor response." This is a bad name, because the muscles which dorsiflex the great toe are physiologically flexor muscles. The term has, however, become so ingrained that we may compromise by referring to it as the so-called " extensor " response. The Babinski sign is really a " fractionated flexor reflex."

The changes in the reflexes and in muscle tone illustrate once more the general law so often alluded to of *release of function in the nervous system.* When a higher centre is destroyed, lower centres are released and exhibit their independent and more primitive activities.

Summary.—The pyramidal tracts form the main connecting-link between the centres for volitional movement in the left hemisphere and the motor nuclei in brain stem and cord. When the pyramidal tracts are destroyed, impairment or loss of voluntary movement occurs. Lower centres are released, resulting in an abnormal posture of the limbs and increase of muscle tone ; exaggeration of the deep reflexes ; the Babinski response from the sole of the foot ; " associated " movements reflexly elicited from the sound to the affected side. The superficial reflexes are abolished. The affected muscles do not waste because, though not used voluntarily, they are in constant reflex activity.

Clinical Conditions Associated with Injury to the Pyramidal Tracts.—It is impossible to enumerate all these conditions, but the main groups are the following :

1. Lack of development or arrested development of the pre-Rolandic area causes Little's disease (spastic diplegia of infants). The gradual death of the Betz cells produces spastic bulbar paralysis and amyotrophic lateral sclerosis. In general paralysis of the insane the cortex generally is affected by the syphilitic virus.

2. Vascular lesions—hæmorrhage, thrombosis, embolism—inflammation,

new growths, may involve the pyramidal system anywhere in its course. The pyramidal tracts are often pressed on in the spinal cord by the distended cavities of syringomyelia.

3. The medullary sheaths of the pyramidal fibres are destroyed in subacute combined degeneration and in disseminated sclerosis.

THE CORPUS STRIATUM

Corpus striatum—Extra-pyramidal tracts—Functions—Effects of disease—Rigidity—Tremor—Disturbance of movement—Summary—Temperature regulation—Clinical conditions.

The Corpus Striatum.—The functions of the corpus striatum and its relation to voluntary movement have been much studied of recent years, chiefly by combined clinical and pathological methods. It is fairly certain that the corpus striatum represents an older motor centre phylogenetically, which has played an important rôle in the past and is still of great functional significance in the lower animals. It is extremely doubtful whether it controls any sort of voluntary movement in man (Kinnier Wilson).

The corpus striatum includes two of the basal ganglia, the *caudate* and *lenticular* [lentiform] nuclei. The optic thalamus represents an older sensory centre, and is not included in the corpus striatum. The lenticular nucleus is subdivided into an external segment, the *putamen*, and an internal and smaller part, the *globus pallidus*. The latter is well developed in fishes, and gives rise to their essential motor mechanism. Its efferent tract myelinates in the early months of intra-uterine life, and is termed the ansa lenticularis. The globus pallidus consists of groups of large multipolar and pyramidal-shaped cells, somewhat resembling anterior horn cells. The caudate nucleus and putamen are chiefly composed of small pyramidal, stellate, or polygonal cells like those found in the sensory centres. The short axons arising from these cells end in the globus pallidus.

The corpus striatum has no known connections with the cortex cerebri. This is a very important observation which seems firmly established. It receives all its afferent impulses from the optic thalamus. The efferent fibres arise solely from the globus pallidus and run as the ansa lenticularis and ansa radiation to the subthalamic region, to end in the substantia nigra and the red nucleus, and probably be linked up with the other motor nuclei of the midbrain and hindbrain.

The tracts arising from these nuclei in the brain stem constitute the *extra-pyramidal* tracts. They probably play an important part in regulating the posture of the body. Their nuclei of origin are influenced by impulses from the cerebellum, the corpus striatum, the vestibular apparatus, the muscles, and perhaps other sources too.

The anatomy of these tracts is as follows (see Fig. 31):

1. The *rubro-spinal* tract arises in the midbrain behind the substantia nigra in the region called the tegmentum. The fibres cross over at once in the decussation of Forel. They lie dorsally in the pons, and then pass forwards to lie in front of the pyramidal tracts in the spinal cord, and end round anterior horn cells. The tract is also known as the pre-pyramidal tract or Monakow's bundle.

2. The *tecto-spinal* tract arises in the superior corpora quadrigemina. The axons decussate at once (decussation of Meynert) to reach the opposite side. Some of the fibres join those of the rubro-spinal tract, but the majority constitute what is called the anterior longitudinal bundle.[1] This mass of white fibres is readily recognized in sections of the brain stem. It lies in the middle line just ventral to the posterior longitudinal bundle and the grey matter in the floor of the aqueductus Sylvii and fourth ventricle, and close to its fellow of the opposite side. It thus passes down through the pons and medulla and enters the antero-lateral region of the cord, to end round anterior horn cells

3. The *ponto-spinal* tract arises from large cells in the pons—the nuclei pontis. Some of the fibres cross to reach the opposite lateral columns of the cord, but many descend in the antero-lateral columns of the same side, to end round anterior horn cells.

4. The *vestibulo-spinal* tract consists of descending fibres from Deiters' nucleus. This is a prominent mass of grey matter lying at the junction of pons and medulla, above and dorsal to the inferior peduncle of the cerebellum. It is connected by collaterals with the vestibular division of the eighth nerve, and thus with the semicircular canals and otolith organ. The axons pass into the middle line and divide into ascending and descending branches. The ascending fibres form the posterior longitudinal bundle, which is situated dorsal to the anterior longitudinal bundle and runs up to the oculomotor nuclei and superior corpora quadrigemina. The descending fibres pass into the antero-lateral columns of the cord and end round anterior horn cells.

It will be noticed that the last three tracts described all lie chiefly in the antero-lateral columns of the cord. They are sometimes collectively referred to as the *antero-lateral descending tract* (of Löwenthal), to distinguish them from the numerous ascending fibres in this region.

Functions of the Corpus Striatum.—We must beware of arguing too closely from the results of animal work. In birds, the pyramidal tracts are absent, and the corpus striatum may possibly be alone responsible for voluntary movements; but with the development of the cerebral cortex the functional importance of the corpus striatum has steadily diminished. In proportion to the bulk of the whole brain, the corpus striatum is considerably smaller in man than in animals, and its functions have to a corresponding extent been taken over by the new higher centres.

We must devote our attention particularly to the *effects of disease* of the corpus striatum in man. Parkinson's disease (paralysis agitans) is generally attributed to disease of this body, and very similar clinical manifestations occur sometimes after epidemic encephalitis.[2]

The principal results of striatal disease are:

1. Rigidity.
2. Involuntary movement—tremor.
3. Disturbances of movement.

[1] The anterior and posterior longitudinal bundles together constitute the *medial* longitudinal bundle [B.N.A.].

[2] According to M'Alpine (*Brain*, 1926, vol. xlix. p. 525), the corpus striatum is little affected in post-encephalitic Parkinsonism; the region mainly affected, according to this worker, is the *substantia nigra* of the midbrain, where the cells are reduced in number and proliferation of the neuroglia is present (cf. p. 112).

1. **Rigidity.**—The rigidity affects mainly the *proximal* parts of the limbs and the big muscle masses. It affects agonists and antagonists alike. The muscles are firm, tense, and show excessive resistance to passive extension or displacement. Though the rigidity is almost universal in its distribution, its incidence is more marked on certain groups of muscles, so that a very characteristic position results. Thus the sterno-mastoids, biceps, and knee flexors are often affected. The head is bent on the chest, the back is slightly flexed, the arms adducted and flexed, the knees bent—in fact a general attitude of *flexion* is present. The rigidity is often so marked that the patient can be passively moved *en bloc* like a statue. It is obvious that rigidity of such a degree must greatly interfere with the ease and rapidity of execution of voluntary movements. Finally, the rigidity may so fix the joints as to make voluntary movement impossible.

FIG. 32.—Case of Severe Parkinson's Disease.

Hand with fist closed voluntarily. On the signal ("open the hand"), the extensors of the fingers, E.F., contract, and the extensors of the wrist, E.W., relax synchronously in spite of rigidity. Note the well-marked tremor. (Kinnier Wilson, *Lancet*, 1925, vol. ii.)

Injecting cocaine into a rigid muscle abolishes the rigidity by paralysing the local sensory nerve endings (Walshe). This suggests that striate rigidity is *reflex* in origin, and is another example of a release phenomenon.

2. **Tremor.**—This symptom occurs very frequently following disease of the corpus striatum. The tremor consists of fairly regular, rhythmical alternating contraction of a muscular group or groups and their antagonists (see Fig. 32). Tremor is not in any way pathognomonic of striatal disease. We shall notice the occurrence of tremor at rest (static tremor) and during movement ("intention" tremor) in connection with cerebellar dysfunction (pp. 88 and 90). It is of frequent occurrence in the senile, and a very fine tremor is found in exophthalmic goitre (p. 156).

The special features of striatal tremor are as follows:

(1) The *rate* of the periodic muscular contractions is fairly constant, averaging about six per second.

(2) The *range* varies from a very fine to a coarse wide movement.

(3) Theoretically any group of muscles and their opposites may be involved. Actually it prefers the more distal and mobile segments of the body, such as the fingers or hand, or lips or tongue. It may consist first of a flexor-extensor movement at the wrist, then a side-to-side movement (radio-ulnar deviation), and later a movement of pronation supination.

CONDITIONS INFLUENCING TREMOR.—(1) If the back of a hand which is in tremor is pricked with a needle, the tremor may cease for many seconds. Temporary inhibition of the tremor may thus result from painful stimuli.

(2) Emotional disturbances sometimes produce an effect, and so does altering the position of the affected part. Patients find out for themselves what they must do, and what attitude they must throw themselves into, temporarily to arrest the tremor.

Nature of Tremor.—During tremor the law of reciprocal innervation holds good, the antagonists relax when the agonists contract. It is a general law that the more fixed and invariable a movement is, the lower is its position on the physiological level. The scratch reflex of the spinal dog consists of a regular series of flexion-extension movements of the hind limb which cannot be modified in respect of rate or rhythm. Tremor, from its low degree of variability, must be the work of a low physiological level. It must be regarded as a release phenomenon. Injury to the corpus striatum frees a lower centre to initiate the discharge of a rhythmic series of impulses to certain muscles. The *raison d'être* of the movement and its biological significance are not known.

Similar tremor has been produced in decerebrate animals by stimulation of the vicinity of the red nucleus. Without emphasizing this work unnecessarily, it appears that the tremor is due to the released activity of a supraspinal centre, possibly situated in the midbrain.

3. **Disturbance of Movement.**—The corpus striatum has often been regarded as a centre for the " cruder " sorts of voluntary movement. According to Ramsay Hunt, the corpus striatum controls " automatic," emotional, and " associated " movements. On pushing the patient forward or backward, equilibrium tends to be lost and the usual compensatory movements are not seen—this illustrates loss of " automatic " movement in Hunt's sense. " Associated " movements are what we have called " movements of co-operation," and both these and emotional movements were said to be lost in striate disease.

More accurate clinical investigation, however, has shown that the above views cannot be accepted. Kinnier Wilson analyses the disturbance of movement which occurs in striate disease as follows :

i. There is relative *weakness* of the muscles, which varies in extent within wide limits, but is quite definite. After carrying out a movement for some time, *fatigue* sets in more rapidly than normal.

ii. The movements are *slow*, irregular, and limited in extent. This is well seen in the case of the interossei on attempting to spread out the fingers. The movement is not readily carried out, and the feebleness and lack of precision are well marked. These defects involve chiefly the *small* muscles, or at any rate are less evident in the larger masses of muscle. The voice is monotonous, the " chanson de langage " is lost. The delicate adjustments of the laryngeal muscles necessary to produce the inflections and modulations of normal speech are lost. There is jerky movement of the eyes on looking to one side.

iii. There is inability to maintain a contraction. If the eyes are screwed up tight, the orbicularis palpebrarum passes into a state of continuous fluttering (" shuddering lids ").

To sum up : it is seen that muscles are affected chiefly in inverse proportion to their mass. All the small muscles are affected whether they are used in highly complex movements (*e.g.* larynx) or in relatively simple movements (*e.g.* interossei). Other features which are frequently present are lessened

range, lessened flexibility and quickness of contraction, ready fatigue, and imperfect maintenance of contraction.

Poverty of Movement.—When at rest the patient with striate disease literally sits still and does not make the spontaneous movements usually shown by normal people. In the case of a man, he never crosses his legs nor does he toy with his lips and chin during conversation; a woman does not twirl her wedding ring.

Cause of Poverty of Movement.—Intelligent patients explain they have no desire to move. Possibly, as every movement must be done with an effort, they prefer to avoid both the effort and the movement—in other words, they voluntarily desist from movement. The rigidity when present is a contributing factor in making movement difficult and irksome, but is not an essential accompaniment of the "poverty of movement."

"*Movements of Co-operation*" (p. 67) (misnamed "associated movements") are often said to be absent. If we take the example given on p. 67 of getting up from a chair, the Parkinsonian patient is usually in the attitude of flexion with bent knees, and so he will have no need to draw his feet in under him before rising. If his legs are passively extended, he *will* bring them in first under the chair, slowly and unequally, it is true, but the movement of co-operation is present. Arm-swinging (p. 67) (another "movement of co-operation") is certainly reduced in striate disease. The movement, however, is not lost; it is largely refrained from because of the sense of effort necessary to carry it out, and it is interfered with by the rigidity which is present.

Emotional Expression.—In striate disease the face is *mask-like* in appearance. The patient, however, can and does laugh or cry. Emotional movements are carried out slowly and less effectively. One patient said, "I used to have a ringing laugh, now I only make a silly noise." So these movements of the "least voluntary" sort are not lost, but impaired from the factors already mentioned, such as the general poverty and clumsiness of movement and the diffuse rigidity of the muscles. There is not an absence of expression but a lack of ease in passing from one expression to another, so that the normal play of the emotions is not exteriorized.

Certain *negative* points must be emphasized:

1. Reciprocal innervation is normally carried out, and the synergic muscles fix certain joints in the most convenient position in the ordinary way.

2. The reflexes, both superficial and deep, are unaffected at first. When the rigidity becomes severe in degree the joints become fixed, and this mechanically interferes with the reflexes.

The ultimate clinical picture in bilateral involvement of the corpus striatum, if the lesion is of adequate size and duration, is one of complete motor helplessness. The rigidity increases and binds down the joints. Speech and swallowing become difficult, and finally impossible. Tremor is usually marked. No true "paralysis," however, is present.

The *globus pallidus* is the oldest part of the corpus striatum (palæostriatum). The putamen and caudate nuclei develop later (neostriatum). To what extent these nuclei when they appeared took over control of the globus pallidus is uncertain. It has been said that the involuntary movements of striate disease are due to the involvement of the neostriatum. This is not yet proven.

Summary.—The view that the corpus striatum is a "centre" for "automatic," emotional, and "associated" movements is not supported by the evidence. The corpus striatum is a simple body morphologically, which has undoubtedly depreciated in functional importance in man. Probably the duties it carries out are quite simple. When it is injured, the motor cortex is still left to control voluntary movement.

1. The corpus striatum is one of the centres which controls tone in the skeletal muscles; if the ganglion is injured, excessive tone develops—*rigidity*.

2. When it is injured, lower centres are released and initiate rhythmic movements or *tremor*.

3. It is impossible to point to any particular class of movement which is persistently or completely lost when the ganglion is out of action. Fine movements of the small muscles are impaired or lost, but this is not characteristic, for these movements are affected in pyramidal disease too. Further study of this question appears to be necessary.

Temperature Regulation.—Evidence has been brought forward that the corpus striatum helps to maintain the normal temperature of the body. If a tube containing hot water is introduced into the corpus striatum, the phenomena of heat loss occur. The blood vessels of the skin dilate, there is increased secretion of sweat, and the rectal temperature falls. Conversely, if cold tubes are introduced, there is general shivering and the skin vessels are constricted (Barbour). To elicit these reactions, however, fluid must be employed which is *several* degrees above or below that of the body; if the corpus striatum were really a delicate thermostat, one would expect it to respond sensitively to minute temperature changes. Probably the centres which were responding in the above experiments were situated some distance away, in the hypo-thalamic region, and this explains why marked temperature changes in the fluid used were needed before responses were obtained. Further, removal of the corpus striatum does not result in loss of temperature regulation.

Clinical Conditions.—The corpus striatum is probably involved in the following diseases:

1. Parkinson's Disease (paralysis agitans), which may be the result of vascular lesions of this region occurring in old people.

2. Encephalitis Lethargica: the corpus striatum is very commonly affected, producing an end result almost indistinguishable from the previous condition, except that it comes on acutely in younger subjects.

3. Progressive Lenticular Degeneration (Wilson): a bilateral affection of the lenticular nucleus associated with multilobular cirrhosis of the liver.

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THE CEREBELLUM

Cerebellum—Histology—Connections—Stimulation—Acute unilateral lesions—Disturbances of posture and movement—Summary—Clinical conditions—Chorea—Athetosis.

The Cerebellum.—It is not possible in the present state of our knowledge to make any very dogmatic statements about the functions of the cerebellum, but it probably guides the cerebral cortex in the carrying out of voluntary movements, and may play an important part in the regulation of posture.

It consists of two lateral hemispheres and a central portion or vermis. The surface of the cerebellum is covered by a grey cortex which is thrown into numerous fine convolutions. In the white matter of the interior of the cerebellum are found masses of grey matter, the *dentate* nucleus in the lateral hemisphere, and a group of three nuclei—the *roof* nuclei, in the vermis which overhangs the fourth ventricle.

Histology of the Cortex.—Three layers are usually recognized in the cerebellar cortex—an outer *molecular*, an inner *nuclear*, and a middle layer of *Purkinje* cells.

1. The *Purkinje* cells are large flask-shaped cells ; their axons pass into the white matter to end in the deep cerebellar nuclei, or to pass out through the middle peduncle to reach the pons and medulla of the opposite side. Their dendrites form a complex tree-like arborization in the molecular layer.

2. The molecular layer contains the basket cells, whose axons connect up a number of Purkinje cells and end in basket-like interlacements round their bodies.

3. The nuclear layer consists of round cells (granules) with large nuclei which practically fill the cell substance. Their axons pass up into the molecular layer, bifurcate, and their mode of termination is not clearly known. Their dendrons end locally in their own layer in tuft-like endings.

4. Afferent fibres can be traced up from the white matter, though their exact origin is not yet certain : the *moss* fibres end in tufts round the dendrons of the granule cells ; the *tendril* or climbing fibres pass into the molecular layer and twine round the dendrons of the Purkinje cells.

The general arrangement of the cerebellar cortex suggests that it functions chiefly as a centre for rearranging, synthesizing, and redistributing afferent impulses. The deep nuclei serve as discharging centres to the musculature.

Connections of the Cerebellum.—A brief account will be given of those connections of the cerebellum which are of importance. The cerebellum is connected to the brain stem by three peduncles—inferior, middle, and superior.

1. The *inferior peduncle* [restiform body] contains (see Fig. 33) :

(*a*) The *tract of Flechsig* (dorsal cerebellar [dorsal spino-cerebellar] tract), which arises from Clarke's column of cells [dorsal nucleus] on its own side of the body. This column lies at the base of the posterior horn of grey matter, and extends through the thoracic and upper lumbar cord, and is also found in a modified form in the other levels of the cord. Round the cells of the column arborize posterior root fibres, carrying impulses from the deep structures (muscles, tendons, ligaments, and joints) of the same side of the body. The tract of Flechsig lies in the dorsal part of the lateral columns

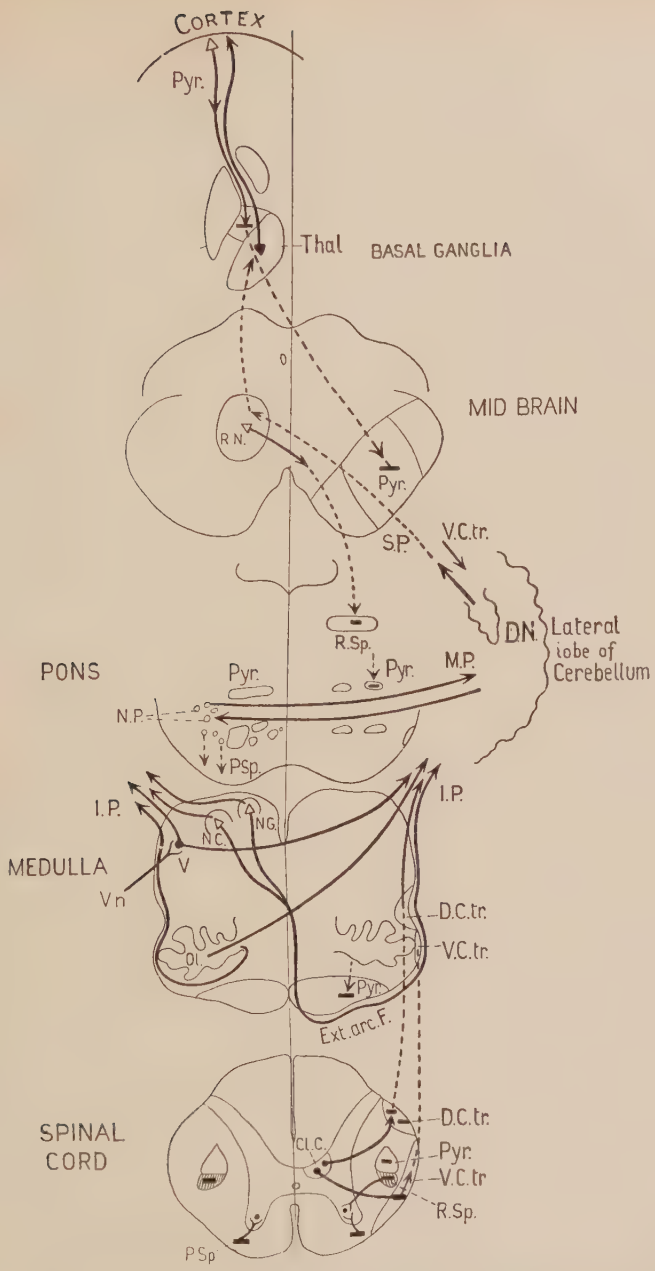

Fig. 33.—Diagram of Connections of Cerebellum.

Pyr. = Pyramidal tract; Thal. = Thalamus; R.N. = Red nucleus; S.P., M.P., I.P. = Superior, middle, and inferior peduncles of cerebellum; V.C.tr., D.C.tr. = Ventral and dorsal cerebellar tracts; N.P. = Nuclei pontis; P.Sp. = Ponto-spinal tract; R.Sp. = Rubro-spinal tract; D.N. = Dentate nucleus; N.C. = Nucleus cuneatus and N.G. = Nucleus gracilis; V.n. = Vestibular nerve; V. = Vestibular nucleus; Ol. = Olivary nucleus; Ext.arc.F. = External arcuate fibres; Cl.C. = Clarke's column.

of the cord, close to its surface, and passes up the inferior peduncle of its own side to end in the vermis.

(*b*) Connections from the *medullary nuclei*, chiefly of the *opposite* side, but partly of the same side. The nuclei concerned are :

i. Vestibular nucleus in which the vestibular division of the eighth nerve has ended.

ii. Olivary nucleus.

iii. Posterior column nuclei (gracilis and cuneatus) in which the tracts of Goll and Burdach have ended.

(*c*) There are a few *efferent* fibres in the inferior peduncle, passing from the cerebellum to the opposite nucleus of Deiters.

2. The *middle peduncle* [brachium pontis] contains :

(*a*) Fibres from the nuclei pontis to the opposite cerebellar hemisphere. Cortico-pontine fibres from the frontal and temporal lobes and collaterals from the pyramidal tracts end in these nuclei, which thus serve to connect the cerebrum of one side with the opposite cerebellum.

(*b*) Fibres coming out from the cerebellum, chiefly from the Purkinje cells and roof nuclei, to reach the pons and medulla of the opposite side.

3. The *superior peduncle* [brachium conjunctivum] contains :

(*a*) The ventral cerebellar [ventral spino-cerebellar] tract (tract of Gowers), which arises from Clarke's column of cells of its own side and transmits impulses from the homolateral deep structures. It lies lateral to the olivary nucleus in the medulla, and finally ends in the vermis of its own side.

(*b*) A large bundle of fibres arises in the dentate nucleus of the cerebellum and forms the superior cerebellar peduncle proper. The fibres decussate in the lower part of the midbrain, and many of them end round the oculo-motor nuclei and round the opposite *red nucleus*. Some proceed on to the *optic thalamus* and are ultimately relayed on to the cortex. The cerebellum thus sends impulses to the *opposite* cerebral cortex. The red nucleus gives origin to the rubro-spinal tract which crosses to supply the anterior horn cells of the opposite side of the cord. Efferent fibres thus go from the cerebellum to the opposite red nucleus and then recross to reach the muscles, so that the cerebellum ultimately controls the muscles of its *own* side of the body.

We may summarize the principal connections of the cerebellum thus :

1. Each cerebellar hemisphere receives impulses from the deep structures (muscles, tendons, ligaments, etc.) of its own side of the body, and from the vestibule (chiefly of the opposite side).

2. By means of its efferents the cerebellum controls the activity of the middle and highest physiological levels.

(*a*) By means of the fibres passing in the superior peduncle to the red nucleus, in the middle peduncle to the nuclei pontis, and in the inferior peduncle to Deiters' nucleus, it controls the activity of the brain stem centres. Because the rubro-spinal tract crosses completely and the ponto-spinal tract in part, the effect is that each cerebellar hemisphere can influence *postural* activity mainly on its *own* side of the body.

(*b*) By means of the connection of the superior peduncle with the opposite thalamus and cortex, the cerebellum influences the highest physiological levels for voluntary movement. As the pyramidal tracts cross to the opposite

side, each cerebellar hemisphere guides and regulates the muscles of its own side during volitional movements too.

Stimulation of the Cerebellum.—Movements result, chiefly of the head and eyes of the same side ; it is easier to elicit movements from stimulation of the deep nuclei than from the cortical grey matter. Some workers attribute these results to spread of current to the nuclei in the floor of the fourth ventricle. A more significant observation is that in the decerebrate animal stimulation of the parts of the vermis which are oldest phylogenetically (the " palæocerebellum "), *inhibits the rigidity* on the same side of the body (Sherrington), and sometimes in all four limbs ; this effect is not obtained from the rest of the cerebellar cortex (see Fig. 34). The path for the reflex appears to be *via* roof nuclei, superior cerebellar peduncle, possibly to the red nucleus. This inhibitory effect which results from stimulation of the vermis is *not* reversed by the injection of strychnine. Though the above results show that the cerebellum may inhibit tone, they do not exclude the possibility of other fibres leaving the cerebellum which may affect tone in another fashion.

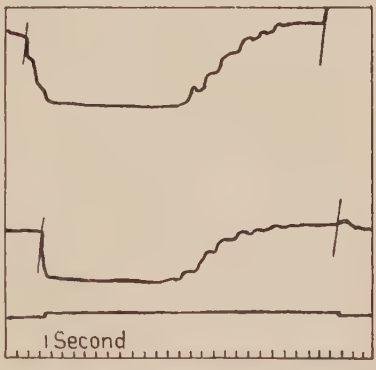

Fig. 34.—Relaxation of Tonic Muscle by Stimulation of the Vermis of the Cerebellum.—After Bremer.

Acute Unilateral Injuries to the Cerebellum.—Extirpation of the cerebellum has yielded very conflicting results. According to Magnus, muscle tone is unaffected by the operation, and the postural reflexes persist (p. 65) and can, in fact, be more readily elicited. Luciani found that for 8 to 10 days after the operation there was heightened muscle tone : opisthotonus, head retraction, extensor spasm of the limbs ; these results suggest that removal of the cerebellum releases centres which were normally kept under inhibition, so that they display increased functional activity. The second stage described by Luciani was one characterized by diminished tone, weakness, and tremor ; but de Barenne claims that atonia, asthenia, and nystagmus (*v. infra*) only develop if the nuclei in the floor of the fourth ventricle, particularly the vestibular nuclei, are injured. No conclusions can yet be drawn from these obviously contradictory results. All workers, however, find that voluntary movements are clumsily carried out.

Acute unilateral lesions of the cerebellum in *man* (*e.g.* as a result of gunshot wounds) gives rise to effects which may be divided, for purposes of description, into two main categories :

1. Disturbances of posture.
2. Disturbances of movement.

Disturbances of Posture.—(*a*) Atonia.—There is diminution or loss of tone in the muscles of the same side of the body, particularly in the limbs. The muscles feel flabby and are readily compressed and displaced ; they can be stretched without producing discomfort. If the patient's forearm be held and the hand shaken to and fro, we find normally that the oscillations

of the hand are definitely limited owing to the tension of the muscles of the forearm. Here the hand swings about like a flail, inertly, till the joints lock and the bony structures prevent further movement. The limbs tend to assume or to be placed in abnormal positions that would be avoided normally. If the patient sits up in bed the weight is thrown to the *dorsum* of the affected hand, so that the fingers and wrist are overflexed to a degree that would be ordinarily painful. Normally, if the forearm be held up vertically, the hand is only slightly flexed. In the case of this injury extensor tone is lost and the hand falls passively into a position of extreme flexion. The symptoms have been mentioned in detail, because they illustrate the varied disturbances following loss of postural activity, and also show how the case should be examined clinically.

(*b*) Attitude.—The face is usually rotated towards the opposite side, and the occiput is approximated to the affected shoulder. The homolateral shoulder is slightly raised and is in front of its fellow of the other side. The leg is abducted and rotated outwards, thus giving the body a wider basis of support. The weight is thrown on the sound leg, and so the trunk is bent with the concavity towards the affected side. Giddiness or vertigo is uncommon, except immediately after the injury, and when present has no constant relation to the side of the injury. In cases of tumour, external objects appear to move away from the side of the lesion and the body tends to follow suit, the head and shoulder, as mentioned above, turning away from the affected side.

(*c*) Spontaneous Deviation.—If the arms are held straight out in front of the body and the eyes closed, they normally remain quite steadily in this position. In cerebellar disease, the homolateral arm sways slowly or quickly away from the symmetrical position and then comes to rest. The deviation is always outwards.

(*d*) Barany's Pointing Test.—The patient lies in bed, and a tape is held above the bed. The patient is asked to touch a certain spot on the tape, then close the eyes, bring the finger down to the bed and then raise it again to the original spot on the tape. As the movement is repeated, the finger gradually deviates outwards. These two phenomena are not due to loss of muscle sense, because the patient is aware of the position of the deviating finger and can touch it with his normal finger. They simply result from the disturbance of postural activity.

(*e*) Static Tremor.—There may be slight oscillations of the head and trunk in any direction, owing to irregular contraction of the muscles which maintain attitude. If the arm is held out, a tremor develops after some time which consists of a slow downward and a quick upward movement. The slow displacement is due to the action of gravity on the tired limb, and the quick jerk is the voluntary effort to get the arm back to its original position.

(*f*) Nystagmus.—Normally the postural mechanism keeps the eyes when at rest in the central position, and when an object is being looked at the gaze is a steady one. In cerebellar lesions the eyes tend to deviate from the central position, some 10° to 30° to the opposite side. Why the deviation is in this direction is not clear, but having gained this position the eyes come to rest and the position is called the "*rest point*." On looking fixedly at an object elsewhere in the visual fields, especially towards the affected side, the eyes display jerking movements termed "nystagmus." In character they

resemble the static tremor described. There is a slow swaying movement towards the rest point, and a quick abrupt recovery, which is of cortical origin. In *tumour* of the lateral lobe the details of the nystagmus are a little different. The slow swaying movement occurs on looking to the *side* of the lesion, and there is a rapid to-and-fro jerking on looking to the opposite side.

(*g*) Alteration of the Deep Reflexes.—As stated, the deep reflexes are a useful index of the state of tone in the muscles. If the time relations of the normal knee-jerk are analysed, it is found that there is a short and decisive rise due to contraction of the quadriceps, a slower, more deliberate fall to the original position, and then the limb comes to rest. The ratio of rise to fall is 1 : 1·2–2·2. In cerebellar lesions the ratio may be 1 : 0·85, *i.e.* the fall is more rapid than the rise. The explanation is as follows : the knee-jerk depends on a proprio-ceptive reflex arc, and is probably a "fractionated myotatic reflex" (cf. p. 53). In response to a stretching force, afferent impulses arise in the quadriceps muscle and pass to the spinal cord by the posterior nerve roots (L3, 4), then to the anterior horn cells, and along the motor nerves to the muscle. A twitch results which brings the knee into the extended position. The twitch is of brief duration, but the limb does not fall limply because of an appended "shortening reaction" (cf. p. 54) which tends to keep the limb in the new position. The relaxation, therefore, is deliberate, and the limb comes to rest. In cerebellar lesions, the twitch may be slower than normal and perhaps less vigorous as well, because the extent of the contraction produced by stretch depends on the initial degree of tone in the muscle, and in cerebellar disease tone is diminished ; nor is there any tendency to maintain the quadriceps in the shortened position, so that the limb falls quite passively when the twitch passes off. If the patient is sat on a high stool, it is found that the leg on falling goes on swinging freely to and fro. This type of response is therefore called the *pendulum knee-jerk* (see Fig. 35.)

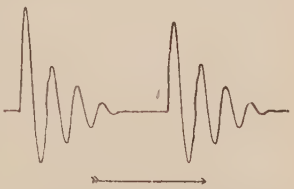

Fig. 35.—Pendulum Knee-Jerk in Cerebellar Disease. (Gordon Holmes, *Lancet*, 1925, vol. i.)

Disturbances of Voluntary Movement.—(*a*) There is feebleness (*asthenia*) of moderate degree, especially in the arm. This becomes more obvious when the movement is prolonged, or requires exertion of much power. The muscles tire very readily, as can be demonstrated by ergograph records. We have already noted that the arm tends to droop if held outstretched for any time.

There is reluctance to move the affected limb, which lies for long periods in one position. Objects are always picked up with the opposite hand ; the affected arm does not swing to and fro in walking. It is even said that when struggling occurs under anæsthesia it is confined to the healthy side.

(*b*) There is *slowness* in executing movements. Graphic records illustrate that there is delay in carrying out every phase of the movement—delay in initiating, in attaining full power, in commencing relaxation, and in reaching full relaxation.

(*c*) *Ataxia* is present—*i.e.* clumsiness and disorderliness of movement. Patients have expressed themselves thus : "My hand will not go straight,

it is drunk ; I do not seem to be able to do what I want with my hand, though if I get hold of anything I can grip it all right " (Holmes). The ataxy is worse if a movement is hurried or if a number of joints are involved. It is not affected by closing the eyes, because muscle sense is perfectly normal and knowledge of position is unimpaired. The ataxy has been analysed thus (Holmes) :

i. *Decomposition of the Movement.*—There is inability to perform simultaneously the various movements which constitute an act. The separate movements are carried out " by numbers " as in a gymnasium. Thus on trying to bring the heel on the opposite knee while lying in bed, the heel is dragged along the bed till it reaches the knee, and then raised to the proper height, then adducted and placed on the knee.

ii. *Asynergia.*—Proper co-ordination is lacking between the agonists, the antagonists, and the synergic muscles which fix joints. Thus the extensors of the wrist are normally synergic muscles to the flexors of the fingers, the former placing the wrist-joint in the most favourable position for the action of the latter. This can be readily seen by attempting to flex the fingers with the wrist horizontal or flexed (p. 67). In cerebellar trouble, on flexing the finger the wrist is extended too late or too early, or not at all.

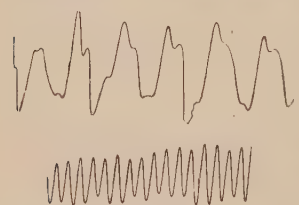

Fig. 36.—Records of Rapid Pronation and Supination of Arm.

Upper curve—on side of cerebellar lesion (showing adiadochokinesis); lower curve—normal side. (Gordon Holmes, *Lancet*, 1925, vol. ii.)

iii. *Dysmetria.*—The force employed is ill adapted to the aim of the movement. The hand shoots past an object or is stopped prematurely.

It is easy to see that the ataxy is due in considerable part to disturbance of function in the highest physiological level, owing to lack of cerebellar guidance. The synergist component of a voluntary movement is imperfectly employed (" asynergia ") ; there is disturbance of the duration of the contraction, the proper timing of one contraction relative to the next (" decomposition "), and the proper force of contraction (" dysmetria ").

These disturbances can be demonstrated by simple clinical tests :

α. Finger-Nose Test.—The patient is asked to bring the tip of the finger of the outstretched hand on to the tip of the nose with the eyes shut. The movement is not begun promptly, the different groups of muscles do not co-ordinate efficiently, the shoulder-joint is not kept still, and the force is not nicely adjusted. The finger thus advances by a series of irregular jerks, the movement being broken up and each phase overdone ; it shoots past the nose, or strikes the nose with excessive force and " keeps on rubbing itself in."

β. Adiadochokinesis.—Rapid pronation and supination is ordered to be carried out simultaneously in both forearms. The movements on the affected side are slower, less regular, and the range is less uniform ; adventitious movements occur at other joints owing to contraction of unnecessary muscles. Because of fatigue and disinclination the movement is soon abandoned (Fig. 36).

γ. Gait.—On first getting out of bed, the whole body sways irregularly, and there is danger of falling to the affected side. The patient feels as if an

invisible hand were pulling him in that direction. After a time, he can maintain his equilibrium fairly well and makes appropriate movements, though clumsy ones, to regain his balance if it be threatened. The gait is frequently described as resembling that of a drunken man. That is inaccurate ; the patient walks carefully ; he does not trust the affected side, taking short steps with that leg and hurrying off it. He deviates spontaneously towards the affected side, and then tries to bring himself back to the original line, thus taking a zigzag path.

δ. Speech.—This is affected in the same way as any other complex movement. It may be slow and monotonous, staccato or scanning in character ; the consonants are frequently blurred, and there is a tendency to explosive utterance. Great efforts are made to utter any sentence, and these are associated with excessive facial grimacing.

After a time, *compensation* occurs, and the movements improve in efficiency. There is less deviation, less decomposition, and better synergia. Excessive force and range persist, however, so that the movements remain jerky in character.

Functions of Cerebellum.—Holmes concludes from his observations on man that by integrating impulses from the muscles and the labyrinth, " the cerebellum plays a part, and probably a controlling part, in the central mechanisms which maintain and regulate postural tone in the muscles. During movement it regulates and co-ordinates the modifications of tone that accompany contraction and relaxation of all groups of muscles directly or indirectly concerned in the movement." Intimately associated with this function, and difficult to consider separately, is the general guidance which the cerebellum exerts over the highest centres for volitional movement.

Clinical Conditions associated with Cerebellar Dysfunction.—Very similar manifestations are found whether the lesion involves the lateral hemisphere or any of the peduncles of the cerebellum between their origin and their termination.

1. In acute irritative lesions (*e.g.* vascular lesions) of the cerebellum, giddiness is severe and forced movements occur, which turn the patient so that his face on the side of lesion is in contact with the pillow.

2. *Tumour* of the cerebellum produces signs closely resembling those already detailed. The nystagmus, as stated, consists of a slow to-and-fro movement on looking to the affected side, and a rapid to-and-fro movement on looking to the opposite side. If the *vermis* is involved, the signs are bilateral and tend to involve the trunk mainly.

3. Tumours growing from the sheath of the *eighth* nerve usually involve the cerebellum later in their course.

4. In *disseminate sclerosis*, plaques of the disease frequently occur in the cerebello-pontine region, and produce signs of cerebellar dysfunction such as nystagmus, " intention tremor," ataxy of speech and of other movements, etc.

5. In a group of diseases called " *hereditary ataxy*," of which Friedreich's disease is the best known, the spino-cerebellar tracts or other cerebellar connections tend to degenerate early, producing characteristic signs.

6. Lesions of the cord, *e.g.* syringomyelia, or tumour, may press on the spino-cerebellar tracts and cause nystagmus, etc.

7. According to Wilson, both *chorea* and *athetosis* are due to loss of cerebellar control and guidance of volitional movement.

In **Chorea,** *voluntary* movement is disturbed in a manner suggesting disturbed cerebellar activity. There is some degree of muscular *weakness*; complaint is made of *uselessness* of the hand; there is a tendency to drop things. The arm hangs limply. Movements are no longer smoothly carried out, but tend to be abrupt and sudden; for example, in response to a command the tongue is suddenly shot out and as rapidly withdrawn.

Fig. 37.—Athetosis.

Hand with fist closed voluntarily. On the signal ("open the hand"), E.F. (extensors of fingers) contract; note tremulous state of muscle at height of contraction. Normally, relaxation of E.W. (extensors of wrist) is synchronous with contraction of E.F. Note here that relaxation of E.W. sets in late, and the muscles then contract although contraction of antagonists continues. (Kinnier Wilson, *Lancet*, 1925, vol. ii.)

Spontaneous movements occur which strongly suggest overactivity of a high physiological level. The movements are complex and elaborate, resemble superficially those executed at the bidding of volition, and appear to be directed to a definite end which, however, is never attained. They also are brief, and rise and fall with peculiar rapidity. As a rule they tend to remain discrete, and reciprocal inhibition of the antagonists is usually present.

Athetosis is very easy to recognize, but is difficult to describe. It consists of spontaneous involuntary movements of a special type. As a rule, the movements are relatively slow and blend with one another, the limb undergoing a series of complex writhings and contortions which accomplish nothing purposeful. Reciprocal innervation no longer holds good. During the movements, agonists and antagonists may contract together and the various synergic muscles may not be brought into play except too late or inappropriately (Fig. 37.) The movements essentially resemble those of chorea; but are slow and confluent in athetosis, discrete and rapid in chorea.

To summarize: 1. The spontaneous movements of choreo-athetosis are highly complex, variable, and ever-changing, suggesting strongly that they are carried out through a high physiological level, *i.e.* the impulses causing the movements are believed to be transmitted *via* the pyramidal tracts. In support of this view we find that the movements cease after the destruction of the motor cortex or of the pyramidal tracts. The movements of chorea demand *relative integrity of the pyramidal tract.*

2. There are striking disturbances of volitional movement—ataxy, weakness, hypotonia—which suggest cerebellar dysfunction.

3. We have repeatedly emphasized the existence of a path from the dentate nucleus to the opposite red nucleus and thalamus. The thalamo-cortical fibres probably radiate to a widespread area of the cortex, especially the post-central and frontal lobes. In this way the cerebellum influences the frontal lobes, where it is suggested that volitional movements are initiated. Owing to loss of cerebellar guidance, voluntary movements are interfered with in the characteristic way.

4. The *spontaneous* movements may be regarded as due to a persistent stream of disordered cerebello-cortical impulses. Or perhaps we may say that a *cortical* reflex arc, with the pyramidal tracts as its efferent path, has been released, with the consequent production of high grade movements comparable to normal volitional movement; but volition neither initiates them nor can it arrest them. They cease, however, during sleep.

Lesions of the thalamus have been repeatedly observed in cases of athetosis and chorea. The cerebello-cortical path may be injured by the rheumatic toxin (Sydenham's chorea); by vascular lesions (post-hemiplegic athetosis and chorea); inflammation (epidemic encephalitis); and in the rare familial affection, Huntington's chorea, by degenerative changes.

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SPEECH

Normal development—Speech diagrams—Broca's centre—Modern views—Aphasia—Pure motor aphasia and alexia—Cortical aphasia—Head's classification—Dysarthria.

Although so much has been written about the physiology of speech and its disorders, it is surprising how comparatively few studies have been made of the development of speech in a normal child. Systematic observation of the child's progress from day to day must be made and noted down in writing, a process which requires much patience and self-denial. Particularly valuable records have been made by Preyer, and especially by Stern. Independently of articulate speech, properly so-called, there are other means by which the child can give expression to its emotions and desires, *i.e.* by crying and laughing, crowing, grunting, facial expression, and gesticulation.

The neurology of laughing, crying, and emotional expression was studied on p. 74. *Crying* occurs as soon as a child is born, and later is much employed as an indication of hunger, wetness, or other forms of discomfort. Gradually the tones of the voice are varied in crying, though the same vowel is employed, so that one can distinguish whether the child is hungry or in pain. *Laughter*—"an audible and visible laugh accompanied by a gleam of the eye"—was observed by Preyer on the twenty-third day; his son laughed

as a sign of joy on looking at his mother's face in the sixth week; he laughed loudly with rapid raising and dropping of the arms in the eighth month.

The *facial expressions* gradually become more diverse. Frowning is noted in the first month, and then the expressions appropriate to fear, rage (with biting, striking out, and stamping), surprise, sulkiness, and feeling of guilt appear. Blushing rarely occurs before the third year.

Gestures.—Shaking the head from side to side as a sign of negation occurs about the thirteenth month; the affirmative nod is not noted till later. The child learns to point correctly in reply to a question or to an object that it wants in the second year.

The above methods of expression are concurrent with the development of speech, towards which the first steps are "automatic" exercises of the speech organs like babbling and crowing. A child kicks and sprawls before it walks, and similarly it makes inco-ordinate noises before talking.

Babbling at first consists of a variety of vowel sounds, namely, *a—a--ah, e -e—e*, etc., and later a number of consonants are introduced too (*g, m, b, d* in the first year; *w, s, z, f, sh* in the second year). *Mimic reading* of books or newspapers is common—the child holds the print before its face and babbles various sounds in imitation of reading aloud (fifteenth month). The child then repeats words it has heard without in the least understanding their meaning (*echolalia*). Usually it repeats the last word of a sentence it has heard, and the word is said over and over again parrot-wise (first year). Later whole sentences may be repeated or recalled from memory without understanding them.

The child soon learns to interpret the various tones of voice, facial expression, and gestures of the people around. *Understanding* of spoken words comes later, and precedes articulate speech. The meaning of "daddy," "mummy," "bottle," etc., are soon learnt (first year). A temporary phase of inventing words may be passed through, *e.g.* Preyer's boy, Axel, said "Momm" when he was hungry. A speaking vocabulary is gradually acquired, *e.g.* thirty-six words at eighteen months, and two hundred words at twenty-one months. First the child learns to name common objects and use words which are frequently heard, *e.g.* "good-night." Later, verbs are employed. Then expressions of sympathy, *e.g.* "poor dolly" are used, questions are asked in increasing number "to the point of weariness." Sentences of greater length and elaborateness are formed at first with elision of syllables and imperfect vowel and consonant sounds, and later more accurately. Correct stressing and grouping of words and definite intonation can be noted. The child at first refers to himself as "he" or by name, *e.g.* Axel, but in the third year he first uses the nominative pronoun "I," *e.g.* "I am coming," instead of "he" or "baby" is coming. Grammatical errors become more rare, and at the end of the third year, the child's speech approximates very closely in intonation to those around him from continually listening to them and imitating them.

The function of speech is a very complex one and involves the highest activities of the brain. To simplify the problem various schemata have been devised to express diagrammatically the events which were thought to occur when speech is carried out. These schemata are of very doubtful validity, but will be briefly described. Certain sounds set up impulses in the eighth nerve and its central connections, and the person hears in his

auditory centre. In the case of words, their sound becomes associated in the mind with certain objects or actions. The meaning of words thus acquired is stored in the *auditory speech* centre in the upper part of the temporo-sphenoidal lobe, especially the first temporal convolution. As regards articulate speech, three neurones were thought to be involved:

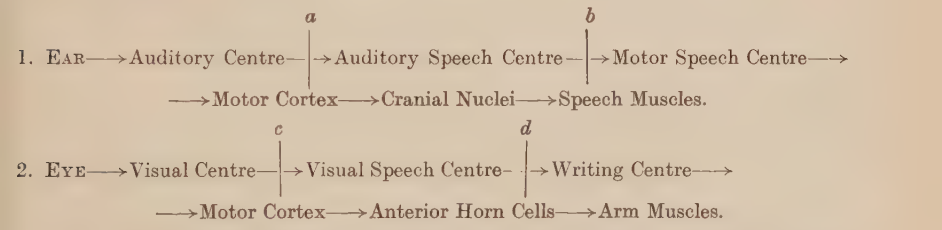
1. The lower motor neurone—the cranial nuclei and nerves which supply the speech muscles.

2. The upper motor neurone—the Betz cells in the appropriate regions of the motor cortex and the pyramidal tracts.

3. As speech involves highly complicated and specialized movements it was suggested that a "super-centre"—Broca's centre, *motor speech* centre—was necessary to control and regulate the motor cortex during articulate speech. This centre was located in the inferior frontal convolution, and was thought to be guided by the storehouse of words and their meaning in the auditory speech centre.

Learning to read and write was thought to depend on a similar process. Written symbols are seen in the visual centre. They become linked up with objects and ideas in the *visual speech* centre, which is situated in the supramarginal and angular gyri. For the execution of written speech a super-centre in the second frontal convolution was postulated, *i.e.* the *written speech* centre, which controlled the arm area of the motor cortex, and indirectly the lower motor neurones in the spinal cord. All the speech centres are found on the *left* side of the brain in normal right-handed people, and on the right side in left-handed people.

These views proved very attractive, as they could be represented in a simple diagram as follows:



The arrows in the diagram represent fibres uniting the various regions. Injuries to the brain could be considered with reference to the diagram, and their effects worked out theoretically. An injury at "*a*" cutting off the auditory from the auditory speech centre destroys the power to understand spoken speech, but does not affect articulate speech—a condition of *sensory aphasia*, or word-deafness. A lesion at "*b*" destroys the power to speak, but leaves understanding unimpaired—*motor aphasia*. A lesion at "*c*" destroys the understanding of written words—*word-blindness*, or *alexia*. An injury at "*d*" abolishes the power to write—*agraphia*. Clinical and pathological study, however, shows that the problem is much more complex than these diagrams suggest.

Broca's Centre.—A reinvestigation of the specimens on the basis of which Broca localized the motor speech centre in the left inferior frontal convolution throws some doubt on his views on the subject. Most of the specimens show widespread lesions involving a great deal more of the brain

than the alleged motor speech centre itself. Histologically Broca's area is different from the motor area of the cortex, and resembles more closely the association regions. According to Pierre Marie, aphasia and lesions of the grey matter of the 3rd frontal convolution are rarely found together. This region has been extirpated in man with no injurious effect on articulate speech (Burckhardt).

P. Marie concludes that the *grey* matter of Broca's area is not related to the speech function. There never appears to have been any very convincing evidence in support of the written speech centre, and it was largely deduced from analogy with the motor speech centre, and these two centres probably stand or fall together.

Modern Views.—Marie denies that there is any distinct localization of function in definite speech centres in the cortex. The speech function must be considered as a whole both on the receptive and expressive side, and both for spoken and written speech.

Marie refers the speech function to a wide area on the left side of the cerebral cortex. As speech is dependent on visual, auditory, and kinæsthetic sensations, the speech centre must be in the closest anatomical connection with the regions of the cortex subserving these functions. Marie includes in the speech area the whole of the temporo-sphenoidal lobe, much of the parietal lobe as far back as the supramarginal and angular gyri, the island of Reil, and perhaps the lower frontal convolutions. This region is a great sensory and association area, and is of course not used solely for purposes of speech. It is the " seat of the intelligence," and any injury to this region depresses the speech faculty as a whole, and also our other highest developed activities. All cases of aphasia due to injuries of the grey *cortex* will show some interference with both the expressive and the appreciative side of speech. Thus simple sentences may be understood, while those involving more complex ideas cannot be followed. The patient may obey when told to raise his hand, but does not know what to do if asked to touch his right hand with his left forefinger.

It is now widely held that there is a widespread area on the left side of the brain concerned with the function of speech, and it is not divided into a series of compact compartments or " centres." This speech area has two great incoming paths—an auditory entering the deep region of the temporal lobe, and a visual which enters near the angular gyrus. Probably the kinæsthetic impulses (from the deep structures) which end in the parietal lobe are very important too. There is a great outgoing path to the Rolandic areas on both sides, and these fibres may pass close to or under the grey matter of the third frontal convolution.

Pure Motor Aphasia is a clinically true condition in which there is loss of articulate speech without mental confusion or deterioration. The patient is dumb, and yet the executive mechanism of speech is intact. The condition is probably a special example of *apraxia* (p. 69); a certain highly complicated group of movements, *i.e.* those of speech, are lost. It is probably due to a lesion, *subcortical* in position, which cuts off the speech area from the Rolandic cortex. The motor cortex does not receive those complex and detailed instructions without which speech movements cannot be executed.

Pure Word-Blindness also occurs. It is the inability to recognize the meaning of written or printed words, which appear as hieroglyphics. The

patient is unable to read aloud or copy print into writing. Speech otherwise is not disturbed. Word-blindness (alexia) is a special form of visual agnosia ; there is loss of the ability to recognize familiar symbols. It is due to a lesion, subcortical in position, which cuts off the visual centres from the speech area. It is usually situated deep in the substance of the occipital lobe behind the angular gyrus, and often involves the optic radiation which is close by and which is passing from the thalamus to the occipital cortex. Word-blindness is thus often associated with right hemianopia—*i.e.* loss of the right half of the field of vision in each eye.

Pure Word-Deafness, *i.e.* the failure to recognize the meaning of spoken speech with no other defect of speech or intelligence, does not occur clinically.

Cortical Aphasia.—As already explained pure word-blindness and pure motor aphasia are caused by *subcortical* lesions. Injuries to the *cortex* depress speech function as a whole. Lesions situated posteriorly affect more markedly the reception of speech, while those situated anteriorly disturb the execution of speech in the main. The later acquired speech functions tend to drop out before those developed in early life. Propositions cannot be made when ejaculations and emotional expression are still possible ; the latter, being more deeply grounded, persists longer.

Head recognizes four varieties of aphasia :

1. Verbal Aphasia.—There is defective word formation ; words both in internal and external speech are evoked with difficulty. Enunciation is slow and halting ; writing is difficult or almost impossible. Numerous errors are present in articulate speech. This corresponds roughly to motor aphasia and agraphia, and may be regarded as a special form of apraxia.

2. Nominal Aphasia.—There is difficulty in naming letters, words, or objects. Reading is impaired. This occurs especially with lesions of the upper temporal lobe.

3. Syntactical Aphasia, which corresponds to what is usually termed " jargon " aphasia. When we speak aloud we immediately recognize what has been said, and are able to correct any faults made. This " backlash " keeps speech at a high functional level. Similarly, impulses from the functioning muscles keep us informed as to how the movements are executed, and visual appreciation maintains a check on writing. When the speech area is isolated on the afferent side, a voluble jargon results. The patient neither hears nor feels that he has spoken incorrectly ; in these circumstances speech is greatly deranged. The patient becomes excited and very voluble, and speaks in a gibberish from which distinguishable words may be entirely absent. He is usually deemed mad by those around him (Collier).

4. Semantic Aphasia.—Want of recognition of the full significance of words and phrases. This may be regarded as a special variety of ideational agnosia (p. 68).

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Dysarthria.—Dysarthria must be clearly distinguished from aphasia. It is a disturbance of speech due to defects of the executive centres in the cortex and their connections, *i.e.* the Betz cells, pyramidal tracts, cranial nuclei, cranial nerves, muscles; disturbances of tone like rigidity; lack of cerebellar control of postural and voluntary activity. Any of these disorders or a combination of them disturb speech to some extent. Dysarthria is often associated with dysphagia (difficulty in swallowing) and regurgitation of food through the nose. In this condition of dysarthria certain groups of muscles cannot be used effectively for *any* purpose, including that of speech. The clinical varieties may thus be summarized:

1. *Muscles*: paralysis of muscles of face in facial forms of myopathy.
2. *Peripheral nerves*: bilateral facial palsy; diphtheritic neuritis.
3. *Cranial nuclei*: bulbar form of progressive muscular atrophy; tumours of medulla; myasthenia gravis (dysarthria is not present when the patient begins to speak, but then increases rapidly in degree till complete dumbness results. Recovery occurs after rest).
4. *Pyramidal system*: spastic bulbar paralysis; degeneration of cortical neurones in general paralysis.
5. *Cerebellum*: disseminated sclerosis, Friedreich's disease, etc., from inco-ordination of the muscles of articulation. The defect is a combination of slurring, elision, undue separation and reduplication of syllables, and stumbling over syllables.
6. *Extra-pyramidal system*: from rigidity in Parkinson's disease.

THE SPINAL CORD AND BRAIN STEM

THE SPINAL CORD.—Tracts—Segmental distribution—Functions—Complete trans-section—Stage of flaccidity—Spinal shock—Reflex activity—Mass reflex—Failure — Incomplete trans-section — Hemisection (Brown-Séquard Syndrome) – Reaction of degeneration.

THE BRAIN STEM.—Medulla—Cranial nerves—XII., XI., X., and IX.—Pons—Mid-brain—Red nucleus—Tectum—V., III., IV., and VI.—Local lesions.

THE SPINAL CORD [MEDULLA SPINALIS]

WE have already discussed fully the various ascending and descending tracts of the spinal cord. It remains here to summarize the facts briefly.

A. **Descending Tracts.**—1. Crossed pyramidal tract [lateral cerebro-spinal tract]: lies in the lateral columns of the cord. It is derived from the Betz cells of the opposite motor cortex (pp. 69 and 71).

2. Direct pyramidal tract [anterior cerebro-spinal tract]: in the anterior columns close to the anterior median fissure. It does not extend below the mid-thoracic region. The fibres cross in the anterior commissure to end round cells of the opposite side.

3. Rubro-spinal tract (pre-pyramidal tract, Monakow's bundle): lies in front of the crossed pyramidal tract in the lateral columns. It arises in the red nucleus of the opposite side and ends round anterior horn cells (p. 78).

4. Antero-lateral descending tract: this general term includes fibres derived from various sources which lie in the antero-lateral region of the white matter of the cord (p. 79).

(*a*) Tecto-spinal tract, from the superior corpora quadrigemina of the opposite side.

(*b*) Ponto-spinal tract, from the nuclei pontis of the same and opposite sides.

(*c*) Vestibulo-spinal tract, from Deiters' nucleus [lateral vestibular nucleus] of both sides.

(*d*) Olivo-spinal [bulbo-spinal] tract (Helweg's bundle), from the olivary nucleus.

These four tracts end round anterior horn cells.

B. **Ascending Tracts.**—1. Tracts of Goll and Burdach [funiculus gracilis and funiculus cuneatus], in the posterior columns of the cord. They arise in the posterior root ganglia of their own side of the body, and end in the nuclei gracilis and cuneatus in the medulla. The tract of Goll lies mesial to the tract of Burdach. The tract of *Lissauer* [postero-lateral tract] consists of short ascending fibres of the posterior nerve roots.

2. Dorsal Cerebellar [Spino-Cerebellar] Tract (direct cerebellar tract, tract of Flechsig) arises in Clarke's column of cells [dorsal nucleus] of its own side, and passes up the inferior peduncle to end in the vermis of the cerebellum. It lies on the surface of the lateral region of the cord.

3. Antero-Lateral Ascending Tracts.—It must be remembered that this region of the cord contains a medley of ascending and descending fibres with varying origins and different destinations. The two principal ascending groups of fibres are :

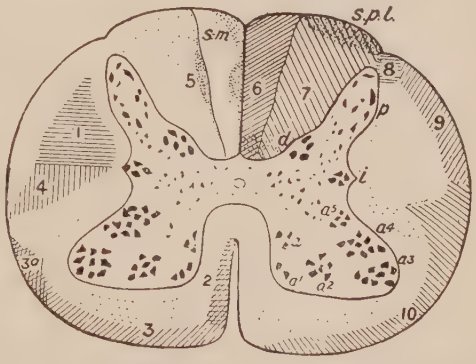

Fig. 38.—Diagram showing the Ascending (right side) and Descending (left side) Tracts Spinal Cord.—Sharpey-Schafer.

1. Crossed pyramidal tract; 2. Direct pyramidal tract; 3. Antero-lateral descending; 3*a*. Bundle of Helweg; 4. Rubro-spinal; 5. Comma; 6. Tract of Goll; 7. Tract of Burdach; 8. Lissauer's tract; 9. Dorsal cerebellar (Flechsig); 10. Spino-thalamic and ventral cerebellar; *s.m.* Septo-marginal; *s.p.l.* Superficial dorso-lateral fibres; a–a^5. Cells in anterior horn; *i*. Cells in lateral horn of grey matter (connector cells of sympathetic); *p*. Cells of dorsal horn; *d*. Clarke's column of cells. The scattered dots indicate the situation of "endogenous" fibres (arising in the grey matter of the cord) and having for the most part a short course. Many of these which lie near the grey matter have not been indicated.

(*a*) Ventral cerebellar [spino-cerebellar] tract (indirect cerebellar tract) from Clarke's column of cells of the same side, and through the superior peduncle to the vermis of the cerebellum.

(*b*) Spino-thalamic tract: from posterior horn cells of the opposite side of the cord. These fibres cross obliquely in the posterior or anterior commissure to the opposite antero-lateral region of the white matter, and ascend to end in the lateral nucleus and in the "essential organ" of the thalamus.

C. **Endogenous Fibres.**—These are fibres which both arise and end in the cord, and serve in this way to unite different segments, *e.g.* comma [interfascicular] tract and septo-marginal tract in the posterior columns (see Fig. 38).

SEGMENTAL DISTRIBUTION IN THE SPINAL CORD (Collier and Adie)

Segment.	Muscles.	Reflexes.
C4	Spinati.	
C5	Deltoid, biceps [biceps brachii], brachialis anticus [brachialis], supinator longus [brachio-radialis].	Biceps and supinator-jerk.
C6	Pronators of forearm.	Pronator-jerk.
C7	Triceps, extension of wrist and fingers.	Triceps-jerk.
C8	Flexors of wrist and fingers.	
Th1	Small muscles of hand.	
Th2–10	Intercostal muscles.	
Th7–12	Muscles of abdominal wall.	Abdominal reflexes.
Th12–L3	Psoas.	L2, cremasteric reflex.
L3	Adductors of thigh.	
L4	Quadriceps, abductors of thigh.	Knee-jerk.
L5	Hamstrings.	
S1	Glutei, posterior calf muscles.	Ankle-jerk.
S2	Anterior tibials, peronei, small muscles of foot.	Plantar reflex.

The above table is of great importance clinically in the diagnosis of the level of a lesion of the spinal cord.

Complete Trans-section of Cord.—The account which follows is based on Head and Riddoch's work on cases of spinal injury occurring during the Great War, but the accidents of civil life or acute transverse section following on inflammatory or vascular lesions present very similar phenomena ; practically identical results are seen, too, in the experimental animal. In *acute* trans-section of the cord, the patient feels himself cut in two. The higher centres are unaffected and the mind remains quite clear, but the whole of the body *below* the level of the lesion is deprived of all activity.

Stage of Flaccidity.—The muscles are completely paralysed. All the reflexes are abolished and muscle tone is lost. The muscles lie in any position imposed on them by gravity. There is complete loss of all sensation. Cramp-like pains, however, are present at the level of the lesion. The bladder and rectum are paralysed. The sphincter vesicæ may be paralysed at first, but frequently retains its functions or recovers very rapidly with consequent retention of urine (see micturition, p. 143). The penis is flaccid, and erection is impossible. The blood pressure falls, because the tonic impulses from the vasomotor centre cannot reach the cord below the trans-section, and so large areas of the peripheral resistance lose their tone. As all the vasomotor fibres leave the cord between Th1 and L2, it follows that trans-section below L2 will produce very little fall of blood pressure, while section at Th1 causes a maximum lowering of the pressure (cf. p. 279).

The venous return from the limbs depends largely on the contractions of the skeletal muscles. The amount of blood reaching a muscle depends too on the functional activity of the part. Owing to the complete immobility of the lower limbs, the blood flow reaching them is decreased and the venous return is impeded. The paralysed parts are consequently cold and

blue. The limbs are liable to swell if any abnormal tilting of the pelvis obstructs the femoral veins.

The skin is dry and is very liable to be affected by serious sloughing bedsores.

If the lesion is at Th6, all impulses coming in from the abdominal viscera are cut off from the brain. Griping sensations or distension of the viscera will not be appreciated.

The above phenomena belong to the " stage of flaccidity." It is obvious that the isolated segments of the spinal cord have lost their power of mediating for reflex functions. To this temporary state, the term " spinal shock " is applied.[1] In looking for the cause of this condition the following facts must be noted :

Spinal Shock.—(*a*) The " shock " does not affect the parts of the spinal cord headward to the injury. The monkey with its cord divided in the thoracic region, goes on looking out of the window and catching flies. It is obvious that the fall of blood pressure is not responsible for shock. The vasomotor fibres going to a part of the peripheral resistance have been cut off from their centre in the medulla ; as a result, vaso-dilatation occurs in the affected regions. But if a sufficiently important part of the peripheral resistance is relaxed, the *general* systemic blood pressure falls in all parts of the body. The fall of blood pressure is equally marked in the headward part of the animal, which does not appear to suffer at all as a result of the trans-section.

(*b*) Operative shock plays no essential part. The method of trans-section is unimportant ; cutting the cord across quickly or tearing it deliberately makes no difference. Furthermore, if the animal is allowed to recover from the shock and then a second trans-section is made a few segments lower down, the reflex activities of the distal end of the cord are quite unaffected by the second operation.

(*c*) The higher the animal is in the scale of development, the more profound and the more lasting is the condition of spinal shock. In the frog it lasts a few moments, in the monkey a few days, while in man it persists for about three weeks. In the higher animals the spinal cord has but few activities which are completely uninfluenced from the higher levels of the brain. The cortical centres and the great sense organs of the head exercise a dominating influence on all the activities, postural and phasic, of the distal segments of the cord. The cord is so dependent on the constant guidance and control of the higher levels of the nervous system that when these directing influences are suddenly cut off, the cord is temporarily " thrown out of gear," and some time must elapse before it regains its primitive powers of independent activity (Sherrington).

The general principle which emerges from this discussion is very important. The nervous system does not consist of a series of isolated units but is a closely-knit and integrated whole. Damage to any part of the nervous system disturbs its smoothness of working, and until compensation has been established, the functional failure is more severe than can be accounted for by the anatomical lesion. We have already noted that immediately after a hemiplegia reflex spinal activities in the paralysed limbs remain in abeyance for some time—tone is lost, and the reflexes are absent. To this depression of

[1] It is noteworthy that no such condition of " shock " follows trans-section of the brain stem in animals.

function in distant parts of the nervous system the term "diaschisis" (Monakow) is applied.

Stage of Reflex Activity.—As the stage of shock passes off, functional activity returns first to smooth muscle. We noted that the sphincter vesicæ (if affected at all) recovers very soon, but the detrusor of the bladder regains its powers more slowly. The consequent retention of urine must be dealt with by catheterization. Tone next returns to the hitherto paralysed blood vessels, owing to the sympathetic centres in the cord beginning to act independently of the vasomotor centre. The blood pressure is thus restored to about its normal level. The isolated segment of the cord can also mediate as a centre for vasomotor reflexes.

Skeletal Muscle.—(*a*) Tone.—The first activities to return in skeletal muscle are the postural. The flexor muscles of the lower limbs now become less flabby and shapeless, appear more rounded, and offer some resistance to the fingers. This returning tone is, of course, reflex in character and is produced by proprio-ceptive impulses entering the cord from the muscles and deep structures. It is worth noting that the isolated cord "favours" the *flexor* muscles and neurones, and this fact will make clear many of the findings. As would be expected from this general statement, the extensor muscles remain flabby for a much longer period and never attain the same degree of tone as the flexors. *All* the muscles, however, are hypotonic, even the flexors themselves. As previously explained (p. 52) reflex posture is largely dependent on "stretch reflexes"; these reflexes are very imperfectly carried out by the isolated spinal cord and need the presence of the brain stem centres (cf. 53). The limbs thus tend to adopt a position of slight flexion, and in consequence of this the paralysis is referred to as "*paraplegia in flexion*"; the posture is feebly maintained and the limbs cannot support the body weight. Unless some intercurrent disease is present, the muscles undergo no wasting, because, though paralysed for voluntary movements, they are in constant reflex functional activity.

(*b*) Reflex Movements ("Phasic" Reflexes).—Spontaneous involuntary flexor movements of the limbs occur. The small toes are separated and raised; the anterior tibials, the hamstrings, recti abdominis, and adductors of the thigh can be felt to harden, but at first their load is too great and they fail to move the limbs. Contraction of these flexor groups of muscles is accompanied by simultaneous inhibition of the extensor muscles of the limbs.

The reflex movement that returns first is the "flexor reflex." To elicit this reflex a *noci-ceptive* stimulus is necessary, *i.e.* a stimulus which tends to injure the part and which causes pain in the intact organism. The reflex is obtained most easily from stimulating the skin or deep structures of the sole of the foot, but the maximum "receptive field" is much wider than this, so that when the cord is fairly recovered stimulation of the leg as high as the groin or perineum is effective. From the latter regions a stronger stimulus is necessary, and the response is less constant in its appearance. The movement consists of dorsiflexion[1] ("upward movement") and abduction of the toes, dorsiflexion of the foot, flexion of the knee and hip, and adduction of the thigh. The antagonistic muscles are inhibited.

The significance of this reflex is clear. It is a withdrawal movement, a

[1] The toes may sometimes plantar flex.

defence reflex, to remove the limb from an injuring force. Furthermore, this reflex enables us to define precisely what we mean by the terms flexors and extensors of the lower limb. All the muscles which are contracted in the flexor reflex are physiological flexors; the antagonists (which contract in the "extensor thrust" reflex (*q.v.*)) are physiological extensors. It should particularly be noted that the *dorsi*-flexors of the toes and ankles are the physiological flexors in that region. The normal plantar reflex (downward movement or plantar flexion of the toes) is a reflex which only appears with the development of the pyramidal tracts and replaces the more primitive reflex. In cases of injuries to the pyramidal tracts the more recently acquired reflex disappears, the primitive response is released and forms the basis of Babinski's sign (miscalled the "extensor" response). The whole flexor reflex is not obtained as a rule clinically, the movement being limited to spreading out of the small toes and the upward movement of the big toe. The hamstrings—as we would expect—can often be felt to harden. (In the normal plantar reflex the tensor fasciæ femoris contracts.) Various signs of pyramidal disease like Gordon's sign and Oppenheimer's sign now become comprehensible. They consist of eliciting the abnormal toe movement from pinching the calf muscles or firmly stroking the front of the tibia. Here the primitive reflex is obtained from the outer parts of the receptive field, as can be done in the spinal man or spinal monkey.

In spinal animals the flexor reflex often spreads to involve the *extensor* muscles of the opposite limb ("*crossed extensor reflex*," p. 20). In man this does not occur. The reflex is either limited to the same limb or produces *flexion* of the opposite limb.

Mass Reflex.—In some cases reflex activity is very easily elicited, and a very widespread reaction is obtained from scratching any point on the lower limbs or the anterior abdominal wall below the level of the lesion. The response obtained consists of:

1. Flexor spasms of the lower extremities and contraction of the anterior abdominal wall.

2. Evacuation of the bladder even when its contents may only be half the amount which must normally be present before reflex emptying occurs (cf. p. 143).

3. Profuse sweating below the level of the lesion. To appreciate the distribution of the sweating, it must be remembered that the sweat fibres to the head and neck arise from Th1, 2, and those to the arm from Th5–9. With a lesion at the level of Th1, the *whole* body sweats when the mass reflex is obtained, as all the sympathetic fibres leave the cord below the level of the lesion.

Coitus Reflex.—This is produced by stimulation of the glans penis, or the skin round the genitals, anterior abdominal wall, or anterior and inner surface of the thighs. The response consists of swelling and stiffening of the penis, withdrawal of the testes from contraction of the cremaster muscle, and curling up of the scrotal skin from the action of the dartos. The recti abdominis, flexors of the hip, and adductors of the thighs also contract. Seminal emission may occur. On ceasing stimulation, the penis and lower limbs relax.

Reflex evacuation of the *bladder* is gradually established, and the bladder empties itself whenever a certain amount of urine has accumulated in it (cf. p. 143). Reflex defæcation also occurs.

As already stated, reflexes involving the extensor arcs are depressed. The "extensor thrust" reflex can never be elicited in cases of complete spinal trans-section in man.

The *knee-jerk* returns about one to five weeks later than the flexor responses. It consists at first merely of a tightening of the slack quadriceps muscle, but later actual extension of the knee may occur. As pointed out (p. 53), the knee-jerk is a "fractionated stretch reflex"; and such reflexes are not fully seen in the spinal animal. It is therefore found that though the quadriceps may contract fairly briskly it relaxes immediately, and the limb drops quite limply and not gradually as in the normal state (cf. p. 89). The ankle-jerk may return later still. If ankle clonus is present it consists of no more than a few irregular and unequal jerks.

The *skin* hitherto has been dry and scaly, but now sweating returns. The hyperidrosis depends, of course, on intact connection with the sympathetic centres in the spinal cord. The skin becomes more healthy and ulcers heal up rapidly. Because of the improved vascular tone and the return of reflex activity to the skeletal muscles, the circulation through the limbs is greatly improved, and they become warm and of good colour.

Stage of Failure of Reflex Activity.—If general bodily intoxication occurs, failure of reflex function develops. The vitality of the isolated segments of the cord appears to be too low to resist vigorously the action of any baneful influence. The reflexes become more and more difficult to elicit; the receptive fields become narrowed down to the optimum areas from which the reflexes can be obtained. The mass reflex response disappears. The threshold for all reflexes is raised, and fewer groups of muscle are involved in the motor response. The muscles waste and become flaccid, and bed-sores develop, which lower still further the general state of the patient. With each recurrent attack of cystitis the bladder diminishes in size and evacuates itself more irregularly and less completely. As a terminal condition the sphincter vesicæ becomes patulous and the urine dribbles away.

Incomplete Trans-section of the Spinal Cord.—If the spinal cord is gravely injured, but does not suffer complete division, a state of spinal shock develops identical with that already described. When the stage of reflex activity returns, certain striking differences present themselves. To understand these, it must be remembered that in cases of incomplete trans-section some of the descending fibres in the antero-lateral columns of the cord (especially the vestibulo-spinal tract from Deiters' nucleus) have escaped injury, and so some connection between the brain stem and spinal cord is still intact. As we saw in our studies of decerebrate rigidity in which the pons and medulla are left in control of the musculature, these levels of the brain appear to reinforce the activity of the *extensor* neurones. We shall therefore find the greatest evidence of recovery of functional activity in the extensor groups of muscles. Though a hard-and-fast distinction will be drawn here between complete and incomplete trans-section of the spinal cord, it can be readily understood that many intermediate and transitional cases occur.

1. Reflex Tone returns to the extensor muscles, and so the legs lie extended at hip and knee, with the toes pointing slightly downwards. This earns the condition the name of "paraplegia in extension."

2. Involuntary Movements are relatively infrequent, but when they

occur involve an increase of extensor tone, producing downward movements of the feet and toes.

3. Reflex Movements.—(*a*) *Extensor "Thrust" Reflex.*—The lower limb is passively flexed and allowed to rest on the bed. The patient's foot is then pressed up with the palm of the hand. Active contraction of the quadriceps and *posterior* calf muscles (the physiological extensors) occurs, and the limb straightens out. This reflex is of diagnostic importance, because it is never obtained when the cord is completely divided in man. In spinal animals it is obtained quite regularly, as the spinal cord still retains some control over the extensor arcs.

The extension movement is very brief, lasting one-fifth of a second as a rule, but may persist for half a second. It is followed by a refractory period of 1 to 2 seconds during which the reflex cannot be elicited. This reflex is of great importance in locomotion, and exerts considerable force, and is the movement which pushes the body forward in walking. The significance of the refractory period is easy to see. In walking, the extensor movement is followed by a long interval during which the limb is handed over to the flexor groups of muscles, which raise the limb from the ground. During this period the activity of the extensor arcs is in abeyance, as stated above.

(*b*) The *flexor reflex* can be obtained by nocuous stimulation of the sole of the foot. The flexion movement, however, is small, and the receptive field only extends to the knee. It is usually accompanied by active and forcible *extension* of the *opposite* limb (crossed extensor reflex, p. 20).

(*c*) Gentle flexion of one limb produces extension of the opposite limb (Phillipson's reflex). The flexed limb then becomes extended and the opposite one flexed, and so the movement alternates in each limb, producing a "*steppage*" movement (for rôle of stretch reflex in stepping, see p. 53).

We see how the range of reflex response is greater now that more of the nervous system is available. The reflexes described also illustrate well to what an extent the movements of locomotion can be carried out (unconsciously) by the lower levels of the central nervous system.

The extensor *deep* reflexes are perhaps slightly easier to elicit than normal. But the most striking feature of the knee-jerk is the prolonged period of relaxation from the heightened tonic activity in the quadriceps muscle (cf. p. 54).

It is not possible to facilitate emptying the bladder by reflex means when the organ contains less than the adequate amount of urine.

In civil life, though acute trans-section may occur from fracture dislocation of the spine, acute inflammatory lesions, etc., it is much more common to find the cord *compressed*, and gradually increasing trans-section resulting. A common sequence of events when pressure on the cord is produced by tumour is to find (i) *hemisection* of the cord, (ii) *incomplete* trans-section, (iii) *complete* trans-section, occurring in that order. We shall consider the outstanding features of these conditions briefly.

Hemisection of the Spinal Cord (Brown-Séquard Syndrome).—The syndrome is based on the results of clinical observation, and it is customary to assume tacitly that the lesion is of *gradual* development and not of acute onset. The principal phenomena may be classified in this way:

1. Above the Level of the Lesion.—There are no abnormal signs, except possibly a zone of cutaneous hyperæsthesia in the skin area corre-

sponding to the peripheral distribution of the posterior nerve root, which enters the cord just above the level of the lesion.

2. At the Level of the Lesion.—It is frequently not appreciated that the lesion usually involves *several* segments of the cord which have been compressed or destroyed. All nervous elements lying in these segments, or entering or leaving them, will of course be completely destroyed.

(*a*) Destruction of the anterior horn cells results in a "lower motor neurone" type of paralysis in the corresponding groups of muscles. The features of this type of paralysis must be carefully remembered, as the anterior horn cells may be damaged by a great variety of noxious agents, *e.g.* the virus of infantile paralysis, the unknown agent which causes these cells to fall out one by one in progressive muscular atrophy, compression of the cells by the distended cavities of syringomyelia, hæmorrhage within the substance of the cord (hæmatomyelia), pressure of tumours from outside the cord, etc. Division of the anterior nerve root or of the motor fibres in the peripheral nerves also produces identical results.

α. There is complete loss of all movement in the affected muscles.

β. The local reflexes are abolished, including reflex tone, and so the muscles are absolutely flaccid.

γ. The muscles waste: this is usually attributed to loss of mysterious "trophic" impulses from the spinal cord, for it is widely thought that the nutrition of a muscle is controlled by its related anterior horn cell. It is possible, however, that as the nutrition of a part is regulated by its activity, these muscles, which have lost even reflex activity, suffer for this reason.

When the lower motor neurones are injured but still functioning to some extent, certain abnormal electrical reactions are obtained—"*reaction* of *degeneration*." To stimulate the motor nerves in man, one electrode is applied to the "motor point"—the point on the skin which is nearest to where the muscle receives its motor nerve—and the other to some indifferent region such as the back. The induced (faradic) current or the make or break of the battery (galvanic) current may be employed; in the latter case the current may be reversed so that the stimulating electrode may be made anode or kathode at will. Normally stimulation occurs most easily on closing the current with the stimulating electrode as kathode (K.C.C. = kathodal closing contraction) and less easily at A.C.C. (anodal closing contraction). The contractions at break, A.O.C. and K.O.C. (anodal and kathodal opening contraction) are weaker still. When the "reaction of degeneration" (R.D.) is present there is (i) no response to the faradic current, (ii) a slow worm-like contraction to the galvanic current, (iii) A.C.C. is greater than K.C.C. (instead of the reverse). Finally, no contraction may be obtained in response to electrical stimulation.

(*b*) Involvement of the sympathetic nerve cells may cause vasomotor paralysis in the corresponding segments, and the skin may be cold and blue.

(*c*) There is complete anæsthesia for *all* forms of sensation because the posterior nerve roots are destroyed as they enter the cord. The loss of protective pain sensibility exposes the part to injuries which are unattended to, and so whitlows, ulcers, etc., may develop.

3. Below the Level of the Lesion.—(*a*) *Sensory*.—To understand the distribution of the *sensory* loss it must be remembered that "muscle sense" and some touch sensibility ascend the posterior columns of the same side,

while pain, temperature, and part of touch sensibility ascend the antero-lateral columns (spino-thalamic tract) of the opposite side. Touch sensibility will therefore not be lost on either side, but simply be somewhat blunted on both sides. Muscle sense is lost up to the level of the lesion on the same side. The upper limit of the pain and temperature loss on the *opposite* side will *not* correspond to the level of the lesion, because as we saw (p. 36) these fibres cross obliquely in the spinal cord. The level of the lesion will therefore be several segments higher in the cord than would appear from the upper level of pain anæsthesia.

(*b*) *Motor.*—The *motor* phenomena are all on the side of the lesion, and we would expect them to be identical with those found in cases of complete trans-section of the cord. That is not the case however. The explanation is probably this: the Brown-Séquard syndrome is a *clinical* syndrome, and it is very likely that in these cases all connections with the brain stem on the affected side have not been severed, and some extrapyramidal fibres are still unscathed. The clinical picture will therefore be like that in cases of *incomplete* trans-section of the cord: extension of the limb at knee and ankle, spasticity, exaggerated and tonic deep reflexes (knee- and ankle-jerk), ankle clonus, lost superficial reflexes, Babinski's sign present.

If the compression affects both sides more uniformly, we get "paraplegia in extension," as already described (p. 104). The sensory loss first affects posterior column sensibility (sense of position and passive movement), and then temperature, pain, and touch are impaired in that order.

When the trans-section becomes complete, "paraplegia in flexion" develops (p. 102). If infection supervenes all reflex activity in the isolated cord segments is lost, and complete flaccidity is found (cf. pp. 100, 104).

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Head and Riddoch.—*Brain*, 1917, vol. xl. pp. 188–263.
Riddoch.—*Ibid.*, 1917, vol. xl. pp. 263–402.

The Brain Stem

The brain stem includes the medulla, pons, and midbrain, and contains a very large number of important structures very closely packed together. In our studies of the sensory and motor paths we have already noted many tracts traversing or relaying in the brain stem. We shall here correlate these facts and endeavour to obtain a coherent idea of the anatomy and physiology of these very important regions of the brain. The study of the subject will be greatly facilitated by reference to the diagrams (Figs. 39 to 45).

A section through the *lower*[1] *third of the medulla* shows the decussation of the pyramidal tracts. They are seen to pass from the anterior aspect of the medulla through the base of the anterior horn of grey matter, and come to lie in the lateral columns where they descend into the spinal cord. The tip of the anterior horn is thus cut off, and is seen as an isolated mass of grey matter (lateral nucleus) which soon disappears. The posterior columns are wider, and therefore push the posterior horns of grey matter farther apart. The tip of the posterior horn projects on the surface of the medulla as the

[1] In the description of the sections through the brain stem the term "lower" (below) is used to mean *caudal* or posterior; "upper" (above) is equivalent to *cephalad* or anterior.

tubercle of Rolando. In its vicinity is the descending root and nucleus of the fifth nerve, which we shall see in most of our sections because it extends from the pons to the upper cervical region. The central canal of the spinal cord is still situated centrally, but is now beginning to pass nearer the dorsal surface. On the surface in the antero-lateral region on each side are the rubro-spinal tract, the dorsal and ventral cerebellar tracts, and the spino-thalamic tract (cf. p. 40, and see Fig. 39).

A section at the level of the *olivary body* reveals the following points. The central canal is now approaching the posterior surface of the medulla, and is about to open out at the calamus scriptorius into the fourth ventricle. The posterior columns have been replaced by masses of grey matter—the tract of Goll ends in the nucleus gracilis, and the tract of Burdach in the nucleus cuneatus. From the small cells constituting these nuclei a new relay of fibres arises. These take several courses: the majority pass forwards to cross the middle line (internal accuate fibres), and come to lie dorsal to the pyramid as the mesial fillet [mesial lemniscus]. Some fibres pass through the substance of the medulla to both inferior peduncles of the cerebellum, while others (external arcuate fibres) reach the anterior surface of the medulla on the opposite side, and course round the surface of the medulla to enter the inferior cerebellar peduncle.

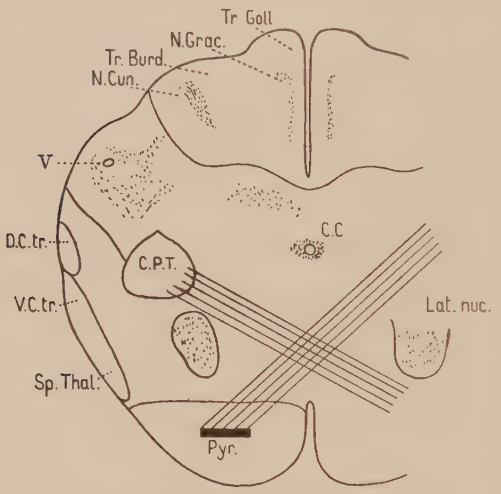

Fig. 39.—Section through Medulla at Level of Decussation of Pyramids (Diagrammatic).

Tr.Goll., Tr.Burd. = Tracts of Goll and Burdach; N.Grac., N.Cun. = Nucleus gracilis, Nucleus cuneatus; V. = Descending root of fifth nerve; C.C. = Central canal; Pyr. = Pyramidal tract; C.P.T. = Crossed pyramidal tract; D.C.tr., V.C.tr. = Dorsal and ventral cerebellar tracts; Sp.Thal. = Spino-thalamic tract.

In the floor of the fourth ventricle at the level of the calamus scriptorius and in close relation to the dorsal nucleus of the vagus are situated certain important centres, *i.e.* cardiac (p. 256), vasomotor (p. 279), part of the respiratory (p. 315), vomiting (p. 405), and deglutition centres.

The olive is seen dorsal to the pyramid. It consists of a wavy layer of grey matter from which fibres run through the hilum to the opposite inferior peduncle. Other fibres form an investment (siliqua) to the olive to reach the same inferior peduncle. Nothing definite is known of the functions of the olive. Its connections with the cerebellum we have just noted; it is believed to give rise to a descending tract—olivo-spinal tract [bulbo-spinal tract] (*Helweg's bundle*), which lies in the cord in the anterior root zone.

The only change to note in the other tracts is that the fibres of touch in the spino-thalamic tract now migrate mesially to lie just dorso-laterally to

the mesial fillet, while the fibres carrying pain and temperature remain external to the olive (see Fig. 40).

The *cranial nuclei* of XII., XI., X., IX., and VII. may conveniently be described here.

XII.—The nucleus of the hypoglossal nerve extends through the lower two-thirds of the medulla. It first lies antero-lateral to the central canal, and when the fourth ventricle appears, it lies in its floor, close to the middle line. The nerve fibres pass out ventrally between the olive and pyramid.

It must be remembered that each hypoglossal nerve pushes the tip of the tongue over to the opposite side. So if the right twelfth nerve is paralysed, the tongue when projected deviates to the right. The affected side of the tongue shows the ordinary signs of a lower motor neurone paralysis — great wasting of the muscle fibres and consequent wrinkling of the mucous membrane.

Fibrillary tremors also occur. We may note here that fibrillation usually occurs in muscles when their corresponding lower motor neurone is undergoing degenerative changes. It is therefore seen in the muscles (including the tongue) when they are first affected in progressive muscular atrophy, in peroneal muscular atrophy, etc. When the lower motor neurone is completely destroyed, fibrillation of the muscles ceases.

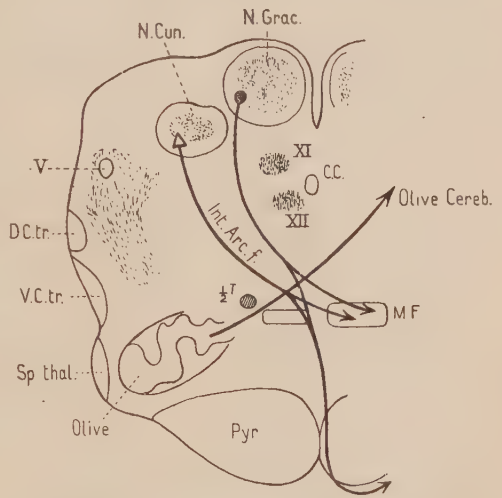

FIG. 40.—Section through Medulla at Level of Olivary Nucleus (Diagrammatic).

Int.Arc.f. = Internal arcuate fibres; M.F. = Mesial fillet; Olive Cereb. = Olivo-cerebellar fibres; ½T. = half touch fibres; XI., XII. = Nuclei of eleventh and twelfth nerves. (For other letters, see Fig. 39.)

XI. — The nucleus of origin of the accessory nerve consists of cells lying in the lateral part of the anterior horn of grey matter in Cl–5.[1] The fibres pass dorsally and then bend outwards to emerge at the side of the cord and medulla as *lateral* roots. These contain large medullated fibres for the supply of sterno-mastoid and trapezius. Fine, medullated, involuntary fibres are also present which join the vagus nerve (p. 123).

X.—The afferent fibres of the vagus arise in the ganglion of the trunk and root from unipolar cells and convey impulses from somatic and visceral (p. 138) structures. Some fibres ascend to end in the *dorsal* nucleus, which lies in the floor of the fourth ventricle lateral to the hypoglossal nucleus. Other fibres descend to form the *fasciculus solitarius* and end in adjacent nerve cells. These two nuclei give rise to the involuntary fibres of the vagus (cf. p. 122) and also connect up with the nucleus ambiguus

[1] The bulbar part of this nucleus (shown in Fig. 40) is best regarded as part of the vagus nucleus (cf. p. 123).

The *nucleus ambiguus* is the voluntary motor nucleus of the vagus, and lies antero-lateral to the dorsal nucleus. The fibres run first dorsally and then curve round to emerge behind the olive and supply such structures as the muscles of the larynx (see Fig. 41).

IX.—The ninth [glosso-pharyngeal] nerve is arranged in exactly the same way as the tenth. The sensory fibres arise in the jugular and petrosal ganglia. They end in nuclei which form the upward continuation of the dorsal nucleus of the tenth (ascending fibres) and the fasciculus solitarius (descending fibres). The motor nucleus supplies the pharynx and is in line with the nucleus ambiguus. The involuntary fibres arise in the dorsal nucleus.

VII.—Though the seventh [facial] nucleus is situated in the lower pons, it must be considered here because the arrangement is like that already described. The afferent fibres arise in the geniculate ganglion and pass in the *pars intermedia* [nervus intermedius] to end in nuclei in line with the dorsal nucleus of ninth and tenth and the fasciculus solitarius. The involuntary fibres arise in the dorsal nucleus (cf. p. 124). The motor nucleus is in line with the nucleus ambiguus. The fibres run backwards and form a loop round the sixth nerve nucleus and then turn forwards and outwards. It has been stated that the fibres supplying the orbicularis oris arise in the twelfth nucleus, and those to the orbicularis palpebrarum in the third nucleus, and are merely conveyed by the facial nerve.

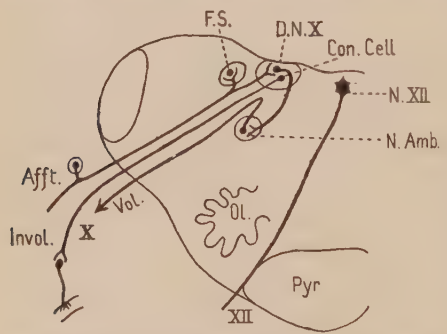

Fig. 41.—Diagram of Mode of Origin of Tenth and Twelfth Nerves.

D.N.X. = Dorsal nucleus X.; F.S. = Fasciculus solitarius; Conn. Cell = Connector cell which gives rise to involuntary fibres in vagus; N.Amb. = Nucleus ambiguus which gives rise to voluntary fibres of vagus; Ol. = Olivary nucleus; Pyr. = Pyramidal tract; N.XII. = Nucleus of twelfth nerve.

In lesions of the pyramidal tract ("supranuclear lesion") voluntary movement in the face is lost, but emotional movements (frowning, smiling) are retained because of the separate emotiona path from the cortex (p. 74). If the seventh nerve is injured in any part of its course ("infranuclear lesion") all movements of the face are equally affected.

We may summarize these facts thus:

XII.: Motor nucleus is a column of cells lying near the middle line.

VII., IX., X., and XI.: 1. Afferent fibres (VII., IX., and X.):

(*a*) Ascending fibres end in a column of cells lying external to nucleus of XII.=column of *dorsal* nuclei of VII., IX., and X.

(*b*) Descending fibres end in grey matter lying just external to the column of dorsal nuclei = *fasciculus solitarius*.

2. Involuntary fibres of VII., IX., and X. arise in the column of dorsal nuclei.

3. Voluntary fibres of VII., IX., X., and XI. arise in one column extending from the lower border of the pons to C5, and situated external and anterior to the column of dorsal nuclei.

A section at the junction of pons and medulla shows the inferior peduncle

and the entrance of the eighth nerve. The central connections of the eighth nerve are fully given on pp. 44 and 59. In Fig. 42 the *cochlear* division is seen to pass dorsal to the inferior peduncle and the vestibular division ventral. The accessory [ventral] nucleus lies between the two divisions of the nerve, and the dorsal nucleus (tuberculum acusticum) on the dorso-lateral aspect of the inferior peduncle. From the former the striæ acusticæ [medullary striæ] cross in the floor of the fourth ventricle, and from the latter the trapezium traverses the substance of the pons. The two groups of fibres turn up as the lateral fillet [lateral lemniscus] lying external to the mesial fillet. The vestibular division ends in the vestibular nucleus (from which fibres to the cerebellum, the red nucleus, and the higher centres arise), and in *Deiters'* [lateral vestibular] nucleus. This latter nucleus has been repeatedly discussed, and we can summarize the various facts we know concerning it. It gives rise to axons which pass to the middle line and ascend to the midbrain as the posterior longitudinal bundle and end in the oculo-motor nuclei; other fibres descend into the spinal cord as the *vestibulo-spinal* tract. It is an important postural centre possibly co-ordinating the position of the eyes and limbs with that of the head. It is the brain-stem centre chiefly responsible for tone in the extensor or "antigravity" muscles and for decerebrate rigidity (p. 50).

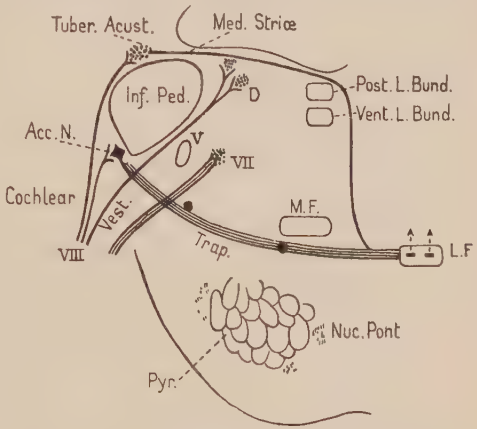

FIG. 42.—Section through the Lower Pons (Diagrammatic).

Med. Striæ = Medullary striæ; Tuber. Acust. = Tuberculum acusticum (dorsal nucleus); Acc. N. = Accessory (ventral) nucleus; Vest. = Vestibular division; D. = Deiters' nucleus; M.F. = Mesial fillet; L.F. = Lateral fillet; Trap. = Trapezium; Nuc. Pont. = Nuclei pontis; Pyr. = Pyramidal tract; Post. L. Bund., Vent. L. Bund. = Posterior and ventral longitudinal bundles; VII, dorsal nucleus of VII.

Other features of the section are:

1. The pyramidal tracts beginning to break up into bundles.

2. The mesial fillet, which is now joined by the spino-thalamic tract conveying the fibres of pain, temperature, and touch.

3. The inferior peduncle of the cerebellum (described on p. 84).

The Pons.—The appearance of the pons is modified by the presence of numerous transversely crossing bundles of the middle peduncle of the cerebellum [brachium pontis] which are running from the pons to the opposite cerebellar hemisphere and *vice versa*. These break up the pyramidal tract into scattered groups of fibres, between which lie small masses of grey matter, the *nuclei pontis*. The mesial fillet is now joined by central fibres from the sensory cranial nuclei. The nuclei pontis give rise to the *ponto-spinal* tracts (Fig. 43).

At the upper border of the pons, the fourth ventricle narrows down gradually into the aqueductus Sylvii [aqueductus cerebri]. Above it on each

side appear two masses of longitudinally running fibres, the superior cerebellar peduncles [brachia conjunctiva]. These arise from the dentate nucleus of the cerebellum, and as they pass forward approach the middle line and decussate to reach the opposite side to end in the red nucleus and thalamus. The ventral cerebellar tract turns over the lateral aspect of this peduncle to enter the vermis of the cerebellum.

The Midbrain [mesencephalon].—The midbrain consists essentially of two structures: the corpora quadrigemina (superior and inferior) behind, and the crura cerebri [cerebral peduncles] in front. Between them is the aqueductus Sylvii, which is surrounded in front and laterally by the nuclei of origin of the oculo-motor nerves.

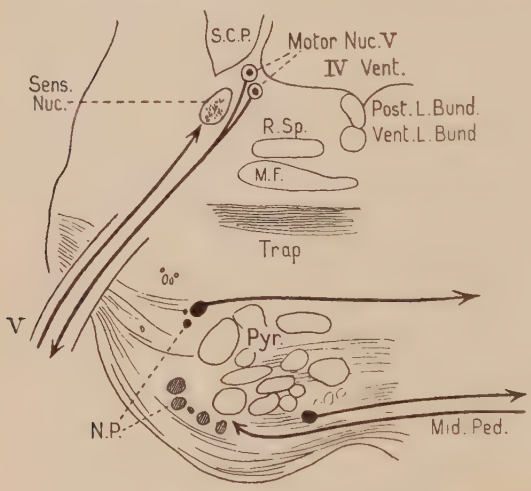

FIG. 43.—Section through Upper Part of Pons (Diagrammatic).

S.C.P. = Superior cerebellar peduncle; V. = Fibres of fifth nerve; IV. Vent. = Fourth ventricle; R.Sp. = Rubro-spinal tract; M.F. = Mesial fillet; Trap = Trapezium; N.P. Nuclei pontis; Pyr. = Pyramidal tract; Mid. Ped. = Middle peduncle of cerebellum; Post.L.Bund., Vent.L.Bund. = Posterior and ventral longitudinal bundles.

The crura are great masses, chiefly of white matter, uniting the pons with the thalamic region of the cerebrum. They consist of three parts from before backwards:

1. CRUSTA OR PES PEDUNCULI, containing fibres from the cerebral cortex to the pons and cord. The middle three-fifths are occupied by the pyramidal tracts; the inner one-fifth by the fronto-pontine; and the outer one-fifth possibly by the temporo-pontine fibres (from lower frontal region and temporal lobes respectively to the nuclei pontis) (see Fig. 44).

2. SUBSTANTIA NIGRA: a mass of deeply pigmented cells, the function of which is uncertain (p. 79). It probably receives efferent fibres from the corpus striatum.

3. TEGMENTUM: a region where longitudinally and transversely running fibres are intermingled in a complex manner. Three decussations take place within it which from below upwards are:

(*a*) Of the superior cerebellar peduncles.
(*b*) Of the rubro-spinal tracts (Forel).
(*c*) Of the tecto-spinal tracts (Meynert).

The Red Nucleus extends from the middle of the ventral surface of the thalamus to the caudal border of the superior corpora quadrigemina (Fig. 20). It consists of two groups of cells: (i) *n. magnocellularis*—composing the caudal third of the nucleus and made up of large nerve cells which give rise to the rubro-spinal tract; (ii) *n. parvocellularis*—which is phylo-

genetically more recent and consists of small cells forming the cranial two-thirds of the whole nucleus. By means of its afferents from the cerebellum and the vestibule and its efferent rubro-spinal tract, it plays an important part in helping to maintain normal bodily posture and normal muscle tone. It is the centre for the " righting reflexes " (p. 63) by means of which the body is restored to its original position after it has been displaced from it. In animals, decerebrate rigidity will only result if the trans-section passes through or below the n. magnocellularis of the red nucleus (p. 50). In man, however, lesions of the pyramidal tract *alone* are sufficient to produce the attitude of decerebrate rigidity. The corpus striatum may influence muscle tone by means of its connections with the rubro-spinal tract.

The path for emotional expression lies in the tegmentum internal to the red nucleus. The lateral fillet passes back to end in the inferior corpora quadrigemina.

The *inferior corpora quadrigemina* [inferior colliculi] were briefly dealt with in discussing the auditory path (p. 45). The *superior corpora quadrigemina* [superior colliculi] are of greater interest. They are an important centre for visual reflexes. By means of the tecto-spinal tract they can alter the position of the eyes, head, trunk, and limbs in response to retinal impulses. *Colliculo-nuclear fibres* pass to the third nerve nucleus to cause constriction of the pupil during the light reflex (p. 47). A long tract (possibly the tecto-spinal tract) connects the superior colliculi with the pupil-dilator centre in the thoracic cord (Th1 and 2).

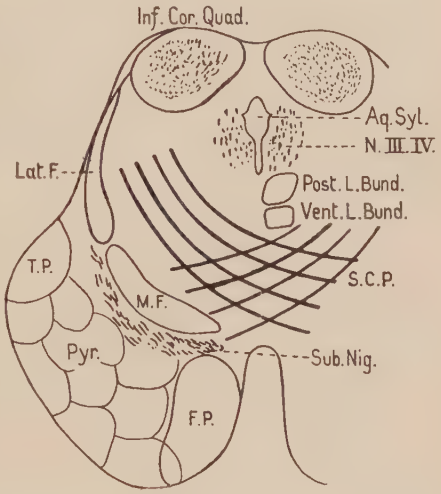

FIG. 44.—Section through Midbrain at Level of Inferior Corpora Quadrigemina (Diagrammatic).

Inf. Cor. Quad. = Inferior corpora quadrigemina; Lat. F. = Lateral fillet; M.F. = Mesial fillet; Aq. Syl. = Aqueductus Sylvii; Post. L. Bund., Vent. L. Bund. = Posterior and ventral longitudinal bundles; S.C.P. = Superior cerebellar peduncle; N. III. IV. = Nuclei of third and fourth nerves; Sub. Nig. = Substantia nigra; T.P., F.P. = Temporo-pontine, fronto-pontine fibres; Pyr. = Pyramidal tract.

We can now complete our study of the cranial nuclei.

V.—[Trigeminal nerve]—The *motor fibres* arise from a nucleus lying at the side of the grey matter bounding the aqueductus Sylvii and fourth ventricle in the lower midbrain and upper pons (Fig. 43).

The *sensory fibres* are derived from the Gasserian ganglion [semilunar ganglion] and end in a mass of grey matter lying lateral to the motor nucleus—the *principal sensory nucleus*. Long descending fibres are given off which end round adjacent grey matter.[1] This column of cells and fibres

[1] Note how the following sensory cranial nerves, V., vestibular division of VIII., IX., and X., end in a principal sensory nucleus and give rise to descending fibres which end in adjacent grey matter.

—*descending root* [spinal tract] of the fifth nerve descends to the upper cervical region of the cord. From these sensory nuclei a new relay of fibres passes across the middle line to join the mesial fillet.

Oculo-Motor Nuclei.—Though we speak of the nuclei of the third [oculo-motor], fourth [trochlear], and sixth [abducens] nerves as if they were isolated structures, it is important to realize that they simply constitute one long column of grey matter controlling the movements of the eyes. This column extends from the upper part of the midbrain surrounding the ventral and outer part of the aqueductus Sylvii (III., IV.), down to the upper part of the pons in the floor of the fourth ventricle (VI.). The fibres of the third nerve take a curved course in the tegmentum to emerge on the inner side of the crus. The fourth nerves decussate in the roof of the aqueductus Sylvii. The sixth nerve passes between the pyramid bundles to emerge at the lower margin of the pons. Two physiological points must be emphasized:

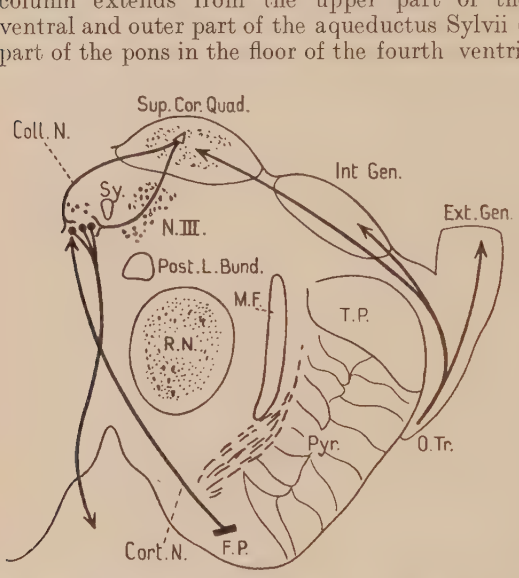

Fig. 45.—Section through the Midbrain at the Level of the Superior Corpora Quadrigemina (Diagrammatic).

Sup. Cor. Quad. = Superior corpora quadrigemina; Coll. N. = Colliculo-nuclear fibres; Sy. = Aqueductus Sylvii; Int. Gen., Ext. Gen. = Internal and external geniculate bodies; N.III. = Nucleus of third nerve; O.Tr. = Optic tract; Post. L. Bund. = Posterior longitudinal bundle; R.N. = Red nucleus; M.F. = Mesial fillet; T.P.—Temporo-pontine; Pyr. = Pyramidal tract; F.P. = Fronto-pontine; Cort. N. = Cortico-nuclear fibres.

1. There are numerous *afferent* fibres in the oculo-motor nerves carrying kinæsthetic impulses from the external eye muscles. These serve to maintain reflex posture in the muscles, and enable the delicate adjustment of gaze during waking hours to be brought about. The cell stations for these afferent fibres appear to lie on the trunks of the oculo-motor nerves.

2. The oculo-motor column on *each* side controls synergic eye muscles on *both* sides. A lesion of the column results, not in paralysis of an individual muscle, but in loss of a movement in both eyes. Enumerating from before backwards, the movements of the eyeballs are controlled by the column thus: (1) pupil-reaction; (2) accommodation; (3) upward movements; (4) downward movements; (5) lateral movements of *both* eyes.

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Local Lesions of the Brain Stem.—Owing to the smallness of the brain stem the symptoms are frequently bilateral from a central lesion

involving both sides. The points to bear in mind are the origins of the cranial nuclei, the long tracts both motor and sensory, and the cerebellar connections. The long paths to and from the trunk and limbs decussate in the medulla; those connected with the face cross in the upper pons. *Crossed paralysis* and crossed anæsthesia are very liable to occur. In the upper pons a lesion may injure the sensory fibres of the fifth, producing anæsthesia of the *same* side of the face, and also involve the mesial fillet with consequent anæsthesia over the *opposite* half of the body. Similarly, a lesion may destroy the fibres of the facial nerve, giving a lower motor neurone paralysis of the face, and also involve the adjacent pyramidal tract, producing an upper motor neurone paralysis of the opposite side of the body. Involvement of the cerebellar connections produces a varying degree of ataxy and other characteristic signs.

To summarize: the symptoms will be a varying combination of paralysis (of both spastic and flaccid type), anæsthesia, and ataxy. The dilator fibres from the midbrain to the thoracic cord (p. 120) must also be borne in mind. Injury to the brain stem may result in small pupils from cutting off the tonic dilator impulses.

II

THE INVOLUNTARY NERVOUS SYSTEM

General arrangement—Sacral autonomic—Sympathetic—Details of distribution and function—Cranial autonomic.
Relation of ductless glands—Adrenal gland—Histology, development, comparative anatomy—Cortex—Medulla—Effects of injecting adrenaline—Site of action—Function—Emergency theory—Cannon's denervated heart preparation—Addison's disease.
Afferent neurones—Area of referred pain and tenderness—Visceral sensibility—Angina pectoris—Visceral reflexes—Respiratory reflexes—Cardiac reflexes—Local nervous reflexes.
Micturition—Nerve supply of bladder—Axon reflex—Postural activity—Voluntary micturition—Effects of trans-section of cord—Other lesions—Obstruction to outflow.

THE INVOLUNTARY [AUTONOMIC] SYSTEM

The study of the involuntary (autonomic) nervous system has been made unnecessarily difficult by the great complexity and confusion of nomenclature which unfortunately exists, and by the attention which is usually devoted to the details of its arrangement, to the neglect of the simple broad principles on which the system is constructed. A few general considerations may help to make these basic principles clear.

If we consider the ordinary spinal reflex arc we can readily recognize that three neurones are involved (see Fig. 46).

1. The afferent or *receptor* neurone (A)—*i.e.* the cell in the posterior root ganglion, and its processes which convey stimuli from the periphery to the central nervous system.

2. The cell in the posterior horn of grey matter which through its axon transmits the impulse to the anterior horn. This may be referred to as the *connector* neurone (B).

3. The anterior horn cell and its axon, or the *excitor* neurone (C), transmits the efferent impulses to a voluntary muscle.

The involuntary nervous system is arranged on exactly the same lines (see Fig. 46).

1. We again have an *afferent* neurone proceeding from an internal organ. The cell station lies in the posterior root ganglion, and a central process is sent into the spinal grey matter.

2. The *connector* cell (Gaskell) is situated not in the posterior horn but in the adjacent grey matter, the exact position differing in the various regions of the nervous system. In the thoracic region, for example, the connector cells lie in the lateral horn of grey matter. The connector fibre must, of

course, connect the afferent neurone with the excitor neurone which actually supplies the viscera. But the excitor neurone is no longer found within the central nervous system. Embryological studies reveal that originally the excitor cells lay close up to the posterior root ganglia, and that later they migrated outwards to form masses of cells situated peripherally. Therefore, to reach the excitor cells the connector fibres must also wander away from the central nervous system to reach these vagrant groups of cells. The connector fibres histologically are medullated or white fibres.

3. The *excitor* cells, as already explained, lie peripherally either as definite ganglia or else as isolated groups of cells. From these cells fibres arise which, by devious routes, must seek out the various organs which they are going to innervate. The excitor fibres are grey or non-medullated nerves.

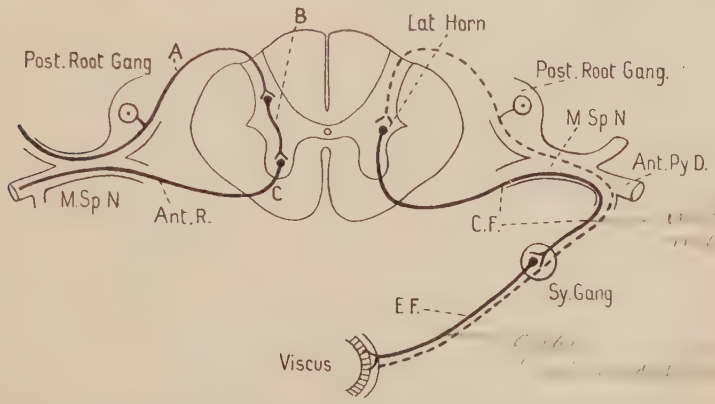

FIG. 46.—General Arrangement of Involuntary or Autonomic Nervous System (on Right) contrasted with that of Voluntary Nervous System (on Left).—After RANSON.

A, B, C. = Afferent, connector, and excitor neurones of voluntary nervous system; Ant.R. = Anterior nerve root; M.Sp.N. = Mixed spinal nerve; Dotted line = Afferent fibre of involuntary system with cell station in posterior root ganglion; Lat. Horn. = Lateral horn of grey matter which gives rise to C.F. = Connector (preganglionic) fibre which passes in anterior, root, mixed spinal nerve, anterior primary division (Ant.Py.D.) to end in Sy. Gang. = Sympathetic ganglion; E.F. = Excitor (post-ganglionic) fibre ending in viscus.

Our knowledge of the afferent neurones of the involuntary nervous system is still very meagre, so we shall discuss first the arrangement of the connector and excitor neurones, using these terms in the sense just defined.

We find that connector cells are not present uniformly in all the segments of the nervous system, but are only to be demonstrated in certain regions:

1. In the brain, in connection with the nuclei of certain of the cranial nerves: *i.e.* III., VII., IX., X., and XI.

2. In the whole of the thoracic region, and in the first two lumbar segments of the spinal cord.

3. In the second and third sacral segments of the spinal cord.

Connector fibres therefore leave the central nervous system from these regions only, and constitute three great systems of outflowing fibres, which are termed the *cranial* (or bulbar), the *thoracico-lumbar*, and *sacral* outflows respectively.

The most useful division of the involuntary nervous system is based on the anatomical situation of the connector cells and fibres. Thus the connector cells in the brain, their fibres in the cranial nerves specified, and their related excitor neurones constitute the cranial division of the system or the *cranial autonomic*. The connector cells in the thoracico-lumbar region, their fibres in the corresponding anterior roots, all their ramifications and their excitor neurones constitute the *sympathetic* nervous system proper. (The use of the term "sympathetic nervous system" to include the whole involuntary nervous system is to be deprecated.) The sacral connector cells, their fibres in the sacral anterior roots, and all their related excitor neurones constitute the *sacral autonomic*.

We can therefore make this classification :

Involuntary or Autonomic System—

A. Cranial Autonomic.
B. Sympathetic proper.
C. Sacral Autonomic.

The cranial and sacral autonomic are referred to collectively by Langley as the *parasympathetic* system.[1]

In describing the anatomical details of the involuntary nervous system it is necessary to note the situation of the connector cells, the path taken by the connector fibres ; the position of the excitor cells, and the path of their fibres. It will be most convenient for us to consider first the simplest division of the system.

Sacral Autonomic System.—The connector cells lie, as stated, in the second and third segments of the sacral cord. Their exact position is not yet known with certainty, but it is probably in the lateral region of the grey matter. The connector fibres pass out in the corresponding anterior roots and then leave these roots to unite to form a single nerve on each side called the pelvic nerve or *nervus erigens*. They proceed into the pelvis to reach the excitor cells which are found in the vicinity, or in the substance, of the organs they will innervate. The structures thus supplied are the *bladder*, part of the *large intestine*, and the blood vessels of the *penis*. It is not definitely determined how great a part of the large bowel is thus innervated. It is usually said that the sacral autonomic supplies the whole of the colon and rectum, with the possible exception of the cæcum (cf. p. 123). The fibres of the pelvic nerves and their related excitor neurones form a plexus, known as the pelvic plexus, which extends over the surface of the bladder and rectum.

Functions.—The sacral autonomic supplies motor fibres to the bladder, the large intestine, and to certain muscle fibres round the prostate. It stimulates the detrusor muscle of the bladder (thus emptying that organ), and, as

[1] The sympathetic and parasympathetic systems may be contrasted as follows : (1) They are, generally speaking, antagonistic in their action on the organs which they both supply, but some organs are innervated by one division only (*e.g.* uterus, adrenal medulla, and most arterioles from sympathetic only, glands of stomach and pancreas from parasympathetic only) ; (2) the excitor cells of the sympathetic are situated, as a rule, at a distance from the organ innervated, and of the parasympathetic in close proximity to the organs (Meckel's ganglion and the otic ganglion (p. 124) are obvious exceptions to the latter statement) ; (3) certain reactions to drugs : the sympathetic is stimulated by adrenaline, the "motor" fibres only of the system are paralysed by large doses of ergotoxin ; the parasympathetic is stimulated by pilocarpine and paralysed by atropine ; (4) *Both* divisions are first stimulated and then paralysed by *nicotine* (p. 124).

might be expected, it inhibits the antagonist of the detrusor, namely, the sphincter vesicæ internus. Similarly, the colon and rectum are made to contract and the sphincter ani internus is inhibited. Contraction of the smooth muscle round the prostate causes some of its secretion to be squeezed out.

As the name "nervi erigentes" implies, erection of the penis is also produced. Stimulation of these nerves relaxes the muscle coats of the arteries which supply the corpora cavernosa and spongiosa. The out-flow through the dorsal vein of the penis is enormously increased and its blood becomes quite arterial in colour. Erection of the penis is due to the great distension of the blood spaces in the organ, which consequently swells and becomes harder.

Sympathetic Nervous System.—The connector cells of the sympathetic lie in the lateral horn of grey matter in the thoracic region and in the corresponding grey matter in the first and second lumbar segments. The distribution of the sympathetic fibres to the various viscera may now be described.

All the connector fibres pass out in the anterior root corresponding to the segment from which they arise, and then enter the mixed spinal nerve. The latter divides into anterior and posterior primary divisions [anterior and posterior rami], and the connector fibre is first continued in the anterior division, but soon leaves it to form a branch which passes to the lateral sympathetic chain. This branch is the so-called *white ramus communicans*; it is a medullated fibre often referred to as the *pre-ganglionic fibre*, because it is passing to the ganglia of the sympathetic. Using Gaskell's nomenclature, the white ramus is merely a portion of the connector fibre. The connector fibre may end in a ganglion of the lateral sympathetic chain, or pass on to more distantly situated ganglia like those in the neck or abdomen. The excitor (or *post-ganglionic*) fibres which arise from the cells of lateral sympathetic chain pass back to the mixed spinal nerves as the *grey rami communicantes* or non-medullated fibres, and are distributed with the spinal nerves to the periphery.

i. Head and Neck.—The connector cells are situated in the lateral horn of Th1 and 2. The connector fibres pass out in the general way described to the lateral sympathetic chain, and proceed up the annulus of Vieussens, and through the inferior cervical ganglion and the cervical sympathetic trunk, to end in the superior cervical ganglion, where the excitor cells are situated. The path of the connector fibres is common to all the structures of the head and neck, but the subsequent course of the excitor fibres varies with the organ supplied.

1. The fibres to the *eye* proceed along the coat of the internal carotid artery into the skull and enter the cavernous plexus (in the cavernous sinus) Their further course is not known with certainty, but two alternative or complementary routes are favoured: (*a*) in the sympathetic root of the ciliary ganglion, through the ganglion itself (without, of course, relaying therein), and along the short ciliary nerves; (*b*) on to the Gasserian ganglion, the ophthalmic division of the fifth cranial nerve, its nasal [naso-ciliary] branch, and finally in the ciliary nerves to the eye.

The structures in the eye supplied by the sympathetic are:

(1) The dilator pupillæ muscle.

(2) Unstriped muscle fibres in the levator palpebræ superioris, which retracts the upper lid.

(3) Smooth muscle fibres at the back of the eye—Müller's muscle—which is said to push the globe forward.

It follows that stimulation of the sympathetic produces dilatation of the pupil, retraction of the upper lid, and forward bulging of the eye (proptosis or *exophthalmos* as it is called). Conversely, a destructive lesion of the sympathetic leads to constriction of the pupil from the unopposed action of the fibres of the sphincter pupillæ which is supplied by the third nerve; drooping of the upper lids (ptosis) with a resulting appearance of "sleepy lids"; and sinking in of the eye, or enophthalmos.

There is believed to be a centre, situated in the superior corpora quadrigemina, for the control of the sympathetic fibres to the eye. Stimulation of the appropriate region leads to dilatation of the pupil. The path connecting this midbrain centre with the connector centre in the cord may possibly be the tecto-spinal tract, which we have already seen traversing the brain stem as the ventral longitudinal bundle to reach the antero-lateral columns of the spinal cord. It follows that disturbance of the sympathetic innervation of the eye may result from a lesion in the brain stem, the cervical or upper thoracic cord, the upper chest, the neck, or the interior of skull or orbit.

2. For the *cutaneous* structures of the head and neck, excitor fibres pass from the superior cervical ganglion to the four upper cervical nerves, and proceed along them to their cutaneous sensory branches to reach the skin. As regards the skin of the *face*, the excitor supply may run along the coat of the external carotid artery and its branches to the face. The various *glands* of this region certainly get their sympathetic supply *via* the blood vessels. This applies to the buccal, parotid, sublingual, submaxillary, and lachrymal glands, which receive vaso-constrictor and "trophic" fibres.

The skin structures (in all parts of the body) supplied by the sympathetic are:

(1) *Sweat* glands with secretory fibres.

(2) Arrectores pili muscles; the smooth muscle which moves the skin and produces in man the appearance known as goose-skin; the smooth muscle round the orifices of the body, such as the anus and vagina; the retractor penis muscle. Motor impulses are sent to them all.

(3) Blood vessels: the cutaneous arterioles, and probably the capillaries, receive many vaso-constrictor fibres from the sympathetic (p. 292).

The *thyroid* receives secretory fibres from the sympathetic (cf. p. 152). The cell station for the excitor fibres may be in the middle cervical ganglion.

ii. Thoracic Viscera.—The connector cells lie in the third and fourth thoracic segments of the cord. The connector fibres in animals pass to the stellate ganglion;[1] in man they appear to end in *all* three ganglia of the cervical sympathetic. The excitor fibres pass from these in the cardiac branches of the sympathetic to reach the *heart*, accelerating it and increasing its force of contraction. The *bronchi* are dilated by inhibition of the smooth muscle in their walls, through fibres having a similar course. It may be emphasized that there is no convincing evidence that the pulmonary arteries receive any constrictor impulses of any significance from the sympathetic system; the coronary arteries may possibly be *dilated* by the sympathetic (p. 243).

iii. Fore-Limb.—The connector cells lie chiefly in the fifth to the ninth

[1] Which lies, in the cat, in front of the neck of the second rib.

thoracic segments. The connector fibres pass to the lateral sympathetic chain to end in the stellate ganglion (animals) and inferior cervical ganglion (man). The excitor fibres arise here and join the nerves of the brachial plexus (C5–Th1) constituting their sympathetic roots. The excitor fibres reach the limb *via* these spinal nerves and are distributed to the skin structures already named, and also to the *skeletal muscles* (p. 56).

iv. Hind-Limb.—The connector cells lie in Th10–12, L1, 2, chiefly in the lumbar segments. The connector fibres end in the lumbar ganglia or lowest ganglia of the sympathetic chain. The excitor fibres arise here and join the lumbo-sacral plexus, and are thus distributed to the lower limb.

v. Thoracic and Abdominal Parietes.—The arrangement in this case is quite simple. The connector fibres arising in the first three thoracic segments pass to the stellate ganglion, from which excitor fibres pass to the upper three thoracic nerves. The rest of the thoracic segments send their connector fibres to the ganglia of the lateral sympathetic chain. The fibres end chiefly in their corresponding ganglia, but also spread up and down the chain to end in adjacent ganglia. Thus one connector fibre may control several groups of excitor cells. From each lateral sympathetic ganglion the excitor fibres pass back in the grey ramus communicans to the corresponding spinal nerve, so that the distribution of the excitor fibres is strictly segmental in character. This is well shown by Langley's studies on the pilo-motor fibres. Stimulation of an anterior nerve root (containing the connector fibres) makes the hairs stand up over several segments of skin. On the other hand, stimulation of the grey rami (excitor fibres) affects solely the hairs of the corresponding spinal segment.

vi. Abdominal Structures.—The connector cells for the abdominal organs lie between Th6 and L2. The connector fibres reach the lateral sympathetic chain in the usual way *via* the white rami. They do *not* relay, however, in the ganglia of the lateral sympathetic chain, but continue through them and leave them as the *splanchnic* nerves, which are therefore still connector or pre-ganglionic fibres. The splanchnic nerves can be divided into two distinct groups: an upper group—the great splanchnic nerves—which connect with the ganglia in the upper abdomen, namely, the cœliac (semilunar), superior mesenteric, renal, spermatic, and ovarian ganglia; and a lower group consisting of the lesser splanchnic nerves which end in the inferior mesenteric ganglia. The upper splanchnics arise from Th6–12, and the lower splanchnics from L1, 2 chiefly. From the groups of ganglia mentioned, grey excitor fibres arise which pass along the big arteries to supply the coats of the vessels themselves and the organs which they reach. Thus we find excitor fibres running with the superior mesenteric artery to the small and part of the large intestine; with the renal artery to the kidney; and along the branches of the cœliac axis to the spleen and liver. The pelvic viscera—*e.g.* the bladder, the uterus, and the distal part of the large intestine—are innervated from the inferior mesenteric ganglia.

(*a*) *Stomach and Intestines.*—There is no doubt that the sympathetic supplies the whole of the small and large intestine and the related sphincters—the ileo-colic and the internal anal sphincters. The extent of the sympathetic distribution to the stomach is not so precisely established. It supplies the pyloric sphincter, the pyloric region of the stomach, and probably to the cardiac sphincter (Carlson). Whether there is any sympathetic

supply to the body of the stomach is doubtful. There are apparently no sympathetic fibres to the œsophagus. Electrical stimulation of the splanchnic nerves results in inhibition of the peristaltic movements of the wall of the gut and diminution of its tone. The sphincter musculature is stimulated and the sphincters become tightly closed.

(*b*) *Blood Vessels.*—The sympathetic conveys vasomotor fibres to the arterioles constituting the splanchnic area. The vast majority of these fibres are vaso-constrictor in character, though a few vaso-dilator fibres (to the blood vessels of the kidney, for example) have been demonstrated. The importance of these vasomotor fibres is very great because the splanchnic area forms the main part of the peripheral resistance (see p. 280).

(*c*) *Bladder.*—The detrusor muscle is inhibited and the sphincter vesicæ and trigonal region are contracted by the sympathetic, the arrangement being analogous to that already found in the case of the gut. It should be noted that the excitor fibres to the bladder from the inferior mesenteric ganglion run in a definite nerve on each side—the hypogastric nerve.

(*d*) The *ureters*, *uterus*, *Fallopian tubes*, and *vas deferens* have been shown to receive both motor and inhibitory fibres from the sympathetic. None of these structures, be it noted, is supplied by the sacral autonomic. Secretory fibres are supplied to the *suprarenal* glands, which regulate the discharge of adrenaline from the medulla of the organ. (The relation of the suprarenal gland to the sympathetic is discussed on p. 127.) We have no knowledge of any nervous control of the cortex of the gland.

It may be of interest to note that in the case of all the organs enumerated in this section (*d*), the connector fibres proceed right up to the organ to relay in excitor cells in their substance. A few of the connector fibres to the *bladder* behave similarly (p. 140).

(*e*) Impulses from the sympathetic stimulate the conversion of the glycogen stores of the *liver* into glucose, which passes into the systemic circulation.

(*f*) Motor fibres are sent to the *spleen*, causing it to contract and discharge the red corpuscles stored in it (cf. p. 214); and perhaps also to the *gall-bladder* (p. 394).

Cranial Autonomic System.[1]—Once the position of the connector cells is appreciated, the construction of this section of the involuntary nervous system becomes quite easy to understand. It is best to describe first the arrangement of the involuntary fibres connected with the vagus.

Vagus.—The afferent neurones of the tenth nerve have their cell station in the ganglia of the root and trunk. The central fibres enter the medulla between the restiform body and the olive to end in the dorsal nucleus of the vagus. This nucleus is situated in the floor of the fourth ventricle, external to the nucleus of the twelfth, and contains connector cells for both voluntary and involuntary systems. In other words, it contains the homologues of both posterior horn and lateral horn cells. Certain large cells give rise to fibres ending in the nucleus ambiguus (or voluntary motor nucleus of the tenth), which supplies certain voluntary structures, like the muscles of the larynx. In the dorsal nucleus are found, too, characteristically small connector cells, referred to as the *nucleus intercalatus* (Staderini). These cells give rise to connector fibres which pass straight out in the vagus trunk and wander with this nerve (still as connector fibres) to reach various viscera, where they

[1] Cranial division of the parasympathetic.

end in excitor cells lying in the substance of the organs. It is clear, then, that the connector fibres of the vagus are analogous to the white rami communicantes or pre-ganglionic fibres of the sympathetic. The grey excitor fibres pass direct from their parent cells to the organ innervated (see Fig. 41).

i. Heart.—The excitor cells lie in the sino-auricular and auriculo-ventricular nodes. The excitor fibres supply chiefly the junctional tissue of the heart (p. 254)—*i.e.* the nodes, the bundle of His and its ramifications—and to a lesser extent the musculature of auricle and ventricle. The vagus depresses all the activities of the heart—impulse formation, conductivity, and contractility—with the result that the heart is slowed and its force of contraction diminished (p. 254). According to Anrep, the vagus conveys *constrictor* fibres to the coronary arteries (p. 243).

ii. Constrictor fibres are sent to the smooth muscle in the walls of the Bronchi.

iii. Alimentary Canal.—The vagus supplies the whole of the alimentary canal from the œsophagus down to the cæcum. Some authorities (Gaskell) believe that the vagus ends at the ileo-colic sphincter, others that it may extend farther. In general, the vagus is motor to the muscle of the alimentary canal (p. 406) and relaxes the sphincters (but cf. p. 406). According to Gaskell, Auerbach's plexus (which lies between the circular and longitudinal muscle coats) acts as the excitor neurone of the vagus in the intestine. A definite plexus containing nerve cells is found on the surface of the œsophagus, and the excitor cells lie there. (We noticed similarly in the distal colon a superficial plexus containing excitor cells for the sacral outflow.)

Vagus fibres have been traced to the gall-bladder (p. 394), liver (p. 394), and kidney, the excitor cells lying in the organs named. Its action on the liver and kidney is unknown—it seems very unlikely that it conveys any secretory fibres to these glands.

Secretory fibres to the glands of the *stomach* have been conclusively demonstrated. We may note here that the "gastrin" theory of gastric secretion has been severely criticized (p. 383). In the case of the *pancreas*, too, the vagus plays an important secretory rôle (p. 389).

Eleventh Nerve.—It is convenient to regard the eleventh and tenth as morphologically constituting one nerve. If we trace down the nucleus ambiguus (the voluntary motor nucleus of the vagus) into the spinal cord we find a column of cells lying in the dorso-lateral region of the anterior horn. These cells give rise to the "lateral" roots which come off the upper five cervical segments to supply the voluntary muscles—the trapezius and sterno-mastoid. In the upper two or three cervical lateral roots are a few small fibres which are probably connector fibres that join the vagus trunk to be distributed with it to involuntary structures. The exact origin of these fine fibres is not established, but they may arise from a downward continuation of the dorsal nucleus of the tenth.

Ninth Nerve.—If we trace the nucleus ambiguus upwards, we find the motor ventral nucleus of the ninth which supplies the stylo-pharyngeus and superior and middle constrictors of the pharynx. The dorsal nucleus of the ninth is continuous with the corresponding nucleus of the tenth and, like it, is a double structure—a fusion of "posterior horn" and "lateral horn" cells. The small connector cells of the dorsal nucleus give rise to fibres which pass

by way of the tympanic nerve and the small superficial petrosal nerve to the otic ganglion which constitutes the excitor centre. The grey excitor fibres arise here, and join the auriculo-temporal nerve to reach the *parotid* gland and supply it with secretory and vasodilator fibres. The dorsal nucleus of the ninth for this reason is sometimes called the *inferior salivary nucleus*. It is worth recalling (p. 48) that taste fibres from the posterior third of the tongue enter the brain stem along the glosso-pharyngeal to end in this nucleus. Thus afferent impulses from the mouth can readily initiate a reflex flow of saliva.

Seventh Nerve.—The voluntary motor nucleus of the seventh is in line with the corresponding nuclei of the ninth and tenth. We find a dorsal nucleus containing connector cells (continuous with the column of dorsal nuclei already described), and referred to as the *superior salivary nucleus*. The connector fibres issue in the pars intermedia, join the facial nerve, and go by way of the great superficial petrosal nerve to Meckel's [spheno-palatine] ganglion. The excitor fibres arise here to pass to the *lachrymal* gland by way of the zygomatic nerve, and to the unstriped muscle, vessels, and glands in the *palate* and *naso-pharynx* via the palatine nerves. Other connector fibres leave the facial nerve in the chorda tympani to reach the lingual nerve and end round ganglia in the vicinity of the submaxillary and sublingual glands. From these cells secretory and vaso-dilator fibres to the glands arise.

As the pars intermedia conveys taste fibres from the anterior two-thirds of the tongue to the superior salivary nucleus, another simple reflex arc for the secretion of saliva becomes evident.

Third Nerve.—The connector cells lie in the most anterior part of the oculo-motor nucleus in the floor of the aqueductus Sylvii. The connector fibres which pass out in the third nerve are often referred to as the *midbrain* outflow in contrast with the bulbar outflow in VII., IX., X., and XI. They leave the third nerve to end in the ciliary ganglion, from which excitor fibres arise to pass in the short ciliary nerves to the *ciliary muscle* and *sphincter pupillæ*. The connector cells for the sphincter of the pupil lie in the mid-brain in front of those for the ciliary muscle. It should be noted that the short ciliary nerves also contain sympathetic grey rami to the dilator pupillæ (p. 119).

Action of Nicotine.—Nicotine has been much used to investigate the path of involuntary fibres. It first stimulates and finally paralyses the junction between the connector fibres and the excitor cells. After painting a sympathetic or parasympathetic ganglion with nicotine, stimulation of the white rami (connector fibres) which end in it is without effect, while stimulation of the grey rami (excitor fibres) produces the ordinary results.

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RELATION OF DUCTLESS GLANDS TO INVOLUNTARY NERVOUS SYSTEM

There seems to be little doubt that the activity of the sympathetic system proper is considerably affected by the secretion of certain ductless glands, especially the adrenal medulla and the thyroid.

1. The *thyroid* gland appears to sensitize the whole or part of the sympathetic nervous system. This appears to be the most reasonable way of explaining some of the phenomena of exophthalmic goitre, *e.g.* the retracted upper lids, the exophthalmos, and the dilated pupils. The tachycardia, the moist skin, the raised blood sugar, and raised blood pressure may also be accounted for in this way, but are more probably the result of the increased rate of metabolism (see p. 156).

2. The medulla of the *adrenal* gland is believed to reinforce the activity of the sympathetic nervous system during conditions of stress. So close is the relationship—both functional and anatomical—between the adrenal medulla and the sympathetic that it is most convenient to discuss the gland fully in this place.

The Adrenal (Suprarenal) Gland.—It must first be made clear that the cortex and medulla of the adrenal have very little in common except their anatomical position. The differences in histological structure, in comparative anatomy, and in their embryological development, indicate that these two parts of the gland subserve quite distinct functions in the body.

Histology.—The *cortex* of the gland consists of columns of polyhedral cells with well-marked nuclei; numerous lipoid granules are found in the protoplasm. The cells are arranged in three zones:

1. Outer *zona glomerulosa*, where the cells lie with their long axis parallel to the surface.

2. Middle *zona fasciculata*, which consists of columns which lie vertical to the surface.

3. Inner *zona reticularis*, where the cells are arranged irregularly, leaving wide blood spaces.

The *medulla* is composed of irregularly arranged cells, some polyhedral and others indefinite in shape. The chief peculiarity of these cells is their staining reaction—with chromic acid or its salts the medulla takes on a dark brown stain, and is therefore often referred to as *chromaphil* tissue. The connector fibres of the splanchnic nerve can be traced into the medulla to end round excitor cells, and also round the chromaphil cells themselves without the intervention of another neurone. Large blood spaces pervade the substance of the medulla.

Comparative Anatomy.—In elasmobranch fishes no adrenal gland is present. Lying between the two kidneys is an elongated body—the "interrenal body"—which structurally resembles very closely the mammalian adrenal cortex. In the ganglia of the lateral sympathetic chain are numerous cells giving the chromaphil reaction, and together representing the adrenal medulla. No one studying these structures in the fish would suspect any functional relationship between these two widely dissimilar tissues. Whether the coming together of "cortical" and "medullary" tissue in the mammalian adrenal has been accompanied by any physiological correlation is very doubtful (Swale Vincent).

Embryology.—The adrenal cortex is mesoblastic in origin, and develops from a thickening of the cœlomic epithelium on either side of the root of the mesentery. The adrenal medulla is developed from a mass of cells which first lies close to the posterior root ganglia, and later migrates out to differentiate into sympathetic nervous system and the chromaphil tissue.

Accessory Adrenal Tissue.—Accessory adrenal tissue is found in

various regions in mammals. Common situations for accessory cortical tissue are the retroperitoneum, the surface of kidney and liver, the space between testis and epididymis in the male, and the vicinity of the broad ligament in the female. It has been held that hypernephroma of the kidney (the "Grawitz tumour") originates from cortical adrenal rests in the kidney substance; this is doubtful, however. These tumours are now thought to be carcinomata of the renal cells.

Accessory chromaphil tissue may be found in the sympathetic ganglia, in the carotid body, and in front of the abdominal aorta.

Consideration of the facts enumerated makes it probable that the adrenal cortex and medulla have quite distinct functions. We shall describe first (for convenience sake) the rôle of the cortex, and then deal with the medulla, which really concerns us here.

The Adrenal Cortex.—*Extirpation* experiments have demonstrated conclusively that the cortex is essential to life, and that the medulla is not. If the whole of both adrenal glands is removed, death results (in most animals) in two or three days. The animal becomes weak and uncertain on its legs; the body temperature falls; there is a diminution in the metabolic rate to the extent of about 25 per cent.; a similar lowering of the metabolism is found in Addison's disease (*q.v.*). The metabolic rate may be raised in these cases and in normal subjects by injections of adrenaline, so that the finding mentioned may be due to loss of the medulla. There is increasing weakness which passes into complete prostration, and finally death results from asthenia and cardiac failure. Removal of the medulla of the gland is obviously a very difficult procedure; but attempts have been made to achieve this by slitting the gland open and cauterizing out the medulla. Systematic histological investigation showed that the medulla could be completely destroyed without any serious effects, but that if too much cortical tissue was damaged at the same time, death followed (Swale Vincent). Why the cortex is essential to life is quite unknown, but two of the suggestions that have been brought forward may be considered:

1. The cortex neutralizes toxins, either introduced from without or resulting from ordinary body metabolism. It is thought that such toxins accumulate after removal of the cortex and cause death.

2. There are a number of ill-understood observations which tend to associate the cortex with the metabolism of *cholesterol*. In view of the great importance of the lipoids in the body this theory might explain the necessity for the cortex.

(*a*) The cortex has a higher lipoid content than any other organ or tissue in the body. High cholesterol diets increase the lipoid content of the adrenal cortex. The adrenal cortex enlarges during pregnancy, during which time there is a rise in the blood cholesterol. Animals fed on cholesterol prior to the operation survive double adrenalectomy for a longer period.

(*b*) After extirpation of both adrenals, the blood cholesterol is said to rise. On the analogy of the hyperglycæmia following pancreatectomy it is concluded that owing to the absence of the secretion of the cortex the tissues are unable to utilize cholesterol. Cholesterol accumulates in the blood, and is excreted in large amounts in the bile (Landau, cf. p. 393).

There is no doubt, however, that the cortex is related to the growth and development of the *sex* glands.

Certain clinical data may first be brought forward. Tumours of the adrenal cortex sometimes occur, called cortical hypernephromata. The cells of these tumours closely resemble histologically normal cortical tissue and may be conceived to function (for a time at any rate) as ordinary cortical cells and so result in excessive formation of the active principle. Precocious sexual development or reversion to secondary sex characters of the opposite kind then occur.

Female children with these tumours have been known to menstruate at the age of 2. Male children show precocious growth of the body as a whole, and of the sex glands in particular, resulting in the stocky " infant Hercules " type. The occurrence of male characters in a female subject is well illustrated by the following case (Glynn). A girl aged $16\frac{3}{4}$ began to menstruate at the age of 15 and continued to do so for one year. The periods then ceased. She grew a beard and moustache, hair developed on the thorax and on the linea alba of the abdomen, and she developed a male voice. The external genitals, however, remained feminine in type. Post-mortem a hypernephroma was found, and the ovaries were seen to be fibrotic and showed no signs of ovulation. Gordon Holmes has reported a case in which removal of the tumour restored the feminine physical and psychical characters.

Adult males suffering from these tumours apparently show no sexual abnormalities.

From the very inadequate data at our disposal it is impossible to state whether the cortex acts directly on the sex organs, or whether it merely influences the activity of the sex glands in various directions.

The Adrenal Medulla.—There is little doubt that the adrenal medulla is as closely related functionally as it is developmentally to the sympathetic nervous system. Probably in the resting condition of the body no secretion is discharged from the medulla. In states of bodily stress or emotional strain there is reason to believe that adrenaline is poured into the circulating blood and reinforces the activity of the sympathetic.

We shall describe first the results of injecting extracts of adrenal medulla, or of the pure active principle itself—adrenaline. With few exceptions adrenaline affects all sympathetically innervated structures throughout the body and produces the same changes as would stimulation of their sympathetic nerve supply. We need not describe these results in detail, as it would be mere recapitulation of what we have already discussed (p. 119 *et seq.*).

Briefly stated, the *effects* are :

1. Eye : dilatation of the pupil ; retraction of the upper lid ; protrusion of the eyeball.
2. Heart : acceleration and increased force of the beat.
3. Bronchi : relaxation of the muscle wall.
4. Intestine : inhibition of the intestinal wall and closure of the sphincters.
5. Liver : conversion of glycogen into glucose : contraction of the capsule of *spleen* and the wall of *gall-bladder*.
6. Bladder : relaxation of the detrusor and contraction of the sphincter and trigone.
7. Uterus : varying effects are produced. In the human subject both the virgin and pregnant uterus are inhibited (Gunn).
8. Skin structures ; excitation of arrectores pili and other smooth muscle in the skin. Constriction of the cutaneous arterioles occurs.
9. Splanchnic area : constriction of the arterioles of the splanchnic area.

10. Skeletal muscle : the effects of fatigue are diminished (p. 57).

Certain points, however, must be elaborated in greater detail.

Circulation.—If adrenaline is injected intravenously into animals with divided vagi or with the vagus nerve endings paralysed by means of atropine, a rapid and very marked rise of blood pressure occurs. The rise is sudden in its onset but is of very brief duration, and after a few minutes the blood pressure returns to normal. There is also increased force and frequency of the heart. [Similarly, perfusing the isolated heart with adrenaline causes acceleration and augments the force.] If the vagi are intact, however—as in the normal animal—the rise of blood pressure is much less marked and is accompanied by marked slowing of the heart. The initial rise of blood pressure distends the aorta and stimulates sensory nerve endings in its wall. Afferent impulses pass up the depressor nerve (p. 257) to the vagus centre and reflexly slow the heart. The vagus nucleus in the medulla is also stimulated by the increased intracranial pressure which results from a rise of blood pressure. The slowing of the heart then is due to increased vagal activity which overcomes the tendency of adrenaline to accelerate the heart.

The rise of blood pressure is due to constriction of the arterioles of the splanchnic area and skin and the consequent rise of the peripheral resistance. If any organ is placed in a plethysmograph (p. 280) we can judge of the changes in the vessels of the organ by studying the alterations in volume which are recorded. If the arterioles relax, more blood is contained in the part and the volume increases ; the reverse occurs if the arterioles constrict. Certain important results are obtained by this method. The abdominal viscera—*e.g.* kidney, intestine, spleen—all shrink markedly, and so do the limbs. If the skin is removed from a limb, the constriction is converted into an expansion. In other words, adrenaline constricts the vessels of the skin, but does not produce this effect on the vessels supplying the skeletal muscles ; in fact, these vessels seem to dilate after the injection of adrenaline. These results need not surprise us. Adrenaline would be expected to mimic the action of the sympathetic and so only affect blood vessels with a definite vasomotor supply. There are numerous vaso-constrictor fibres to the vessels of the skin and the splanchnic area, and these vessels are acted on by adrenaline. The pulmonary vessels are unaffected : it is said that the brain vessels constrict if perfused with adrenaline, but this effect is probably too slight to be of significance. None of these vessels has any sympathetic nerve supply of importance. Our evidence concerning the coronary arteries is conflicting, but they appear to be dilated (p. 243).

The general effect of adrenaline is to *redistribute* the blood in the body and adapt the circulation better to cope with conditions of stress. The splanchnic and skin areas, which are of little importance in times of strain, are constricted, and the blood which is squeezed out of these regions is sent under great pressure to the active skeletal muscles, the lungs, the heart, and the brain, which really need more blood at such times.[1]

When adrenaline is administered therapeutically it is given subcutaneously in doses of ℥iij v of a 1 in 1000 solution, which is equivalent to doses of about 0·003 mgrm. adrenaline per kilogram of body weight. Owing to its

[1] In animals under the influence of ether and certain other anæsthetics, injection of 0·001 mgrm. adrenaline per kilogram body weight causes a *fall* of blood pressure. This depressor effect is not observed in the unanæsthetized animal.

local vaso-constrictor action the absorption of adrenaline is slow, and so its concentration in the blood will be smaller than in animal experiments when similar doses are administered intravenously. One finds, as one would expect, that therapeutic doses of adrenaline have little, if any, pressor effect.

Repeated injections of adrenaline into the auricular vein of rabbits has been claimed to produce degenerative changes in the larger arteries and especially in the aorta, owing to the mechanical strain on the vessels which results from the repeated pressor effects. Too much importance need not be attached to these results, because rabbits are notoriously prone to arterio-sclerotic changes from many experimental procedures.

The injection of 1·5 c.cm. of 1 in 1000 solution of adrenaline subcutaneously in man raises the *basal metabolism* by 20 per cent. The minute output of the heart is increased by 90 per cent., partly by increase of rate and partly by increased output per beat. There is little change in the blood pressure in spite of the increased circulation rate, which suggests that the arterioles are *relaxed*. These changes come on within a few minutes of the injection, and persist for about half an hour. Adrenaline increases the metabolism by stimulating oxidative processes in the tissues generally.

A curious effect on the *respiratory* movements is obtained in some animals. During the height of the blood pressure following injection of adrenaline the respiratory movements cease or become very shallow. This may perhaps be due to constriction of the blood vessels supplying the respiratory centre. The *bronchi* are relaxed, and this is the basis of the treatment of the spasm of bronchial *asthma* by subcutaneous injection of adrenaline.

The actions on skeletal muscle are important. Probably the muscles can work to better advantage owing to their improved blood supply. In addition, as shown on p. 57, adrenaline increases the force of contraction of normal and fatigued muscle in response to stimulation through its motor nerve.

The flow of *urine* is diminished because the blood supply to the kidney is reduced from constriction of the renal arteries.

The *sweat glands* appear to be the only structures which, though supplied by the sympathetic, are *not* acted on by adrenaline.

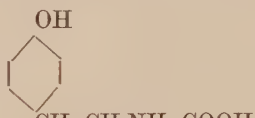
Adrenaline stimulates the conversion of glycogen in the liver (and possibly in the muscles) into glucose, which is then poured into the circulating blood. The level of the blood sugar rises, and if it exceeds the renal threshold some sugar will be excreted in the urine (p. 417). If the liver has previously been emptied of glycogen it is claimed that a rise of blood sugar may still result; possibly adrenaline stimulates sugar formation from protein (cf. p. 398).

The splanchnic nerves carry *secretory* fibres to the adrenal medulla. Stimulation of the peripheral end of the cut splanchnic nerve results in the discharge of adrenaline into the circulation and diminution of the chromaphil material in the gland (see p. 280).

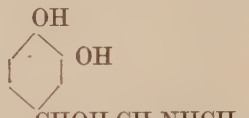
Site of Action of Adrenaline.—There is no doubt that adrenaline acts peripherally and not on the sympathetic nerve centres. Dividing the nerves going to a limb and thereby cutting the contained grey vasomotor fibres in no way alters the constriction of the skin vessels in response to adrenaline. We would naturally be inclined to say that the drug acts on sympathetic nerve endings. That appears not to be the case, however. The crucial experiment consists in extirpating the superior cervical ganglion of the

sympathetic, and allowing time for the post-ganglionic fibres to the eye to degenerate. When the nerve endings have disappeared, adrenaline still exerts its usual effects on the eye. Adrenaline is therefore regarded as acting on a hypothetical " myo-neural substance " or junctional material between the nerve ending and the organ itself. It is remarkable that after " denervation " an organ responds in an even more sensitive manner than normally to adrenaline. In an intact individual instillation of adrenaline into the conjunctival sac has no effect on the pupil ; but after removal of the superior cervical ganglion marked dilatation results from this procedure. Loewi claims that in disease of the pancreas (*e.g.* chronic pancreatitis) local application of adrenaline dilates the pupil in the human subject.

Chemically, adrenaline is a derivative of the amino-acid tyrosine, as will appear from a study of their formulæ :



Tyrosine
p. oxyphenyl-amino-propionic acid.



Adrenaline.

Natural adrenaline is lævorotary ; adrenaline has been synthesized in the laboratory, and the artificial product does not polarize light it is probably a mixture of the lævo- and dextro-rotary forms of adrenaline. It has been shown that lævo-adrenaline is about twelve times as potent as the dextro-rotary form. Adrenaline rapidly disappears from the blood, and probably undergoes a process of oxidation in the tissues.

The Functions of the Medulla.—So far we have merely discussed the action of adrenaline from the pharmacological standpoint, as we would have considered that of any other drug. We must now consider a totally different question : What does the adrenal medulla do in the body ?

1. Under conditions of rest *no* adrenaline can be demonstrated in the circulating blood. We possess extremely delicate tests for the presence of adrenaline ; a piece of intestinal wall suspended in warm oxygenated Ringer's solution contracts rhythmically ; if adrenaline in a dilution of one part in many millions is added to the bath, the muscle relaxes and ceases to contract. Even such a refined method fails to reveal adrenaline in the blood at rest ; but it does show that adrenaline is secreted during states of emotional stress. Clearly the theory which has been widely held that the adrenal medulla constantly maintains the tone of the sympathetic nervous system is quite untenable. The closely related view, that the medulla keeps up the normal blood pressure, is probably equally erroneous, for neither extirpation of the medulla nor tying the adrenal veins (to prevent adrenaline from reaching the circulation) causes any fall of blood pressure. In fact an animal may be kept alive with one adrenal extirpated and only a piece of the cortex of the other gland without any change in the blood pressure.

2. **The Emergency Theory (Cannon).**—Cannon has pointed out the resemblance between the phenomena of emotional stress—the dilated pupil, quickened heart, raised blood pressure, etc. - and the results of sympathetic activity. By various methods it can be shown that adrenaline is secreted in

states of *emotional strain, physical exertion, exposure to cold, asphyxia, under anæsthesia*, on *stimulation of sensory nerves*, and during *hypoglycæmia* (p. 424); the adrenaline poured out stimulates various parts of the sympathetic system, and so enables the body more adequately to meet the crisis.

(i) A fine cannula is passed into the femoral vein and up the inferior vena cava till its upper end lies at the entrance of the adrenal veins. A sample of blood containing the secretion of the adrenal gland can thus be collected in the conscious animal. No adrenaline could be demonstrated in the blood of the "vena cava pocket" at rest, but if the cat is frightened by the barking of a dog adrenaline appears, as shown by the intestinal strip method (p. 130).

(ii) The denervated heart is sensitive to adrenaline in concentrations of 1 400 million; to produce it the stellate and other ganglia supplying sympa-

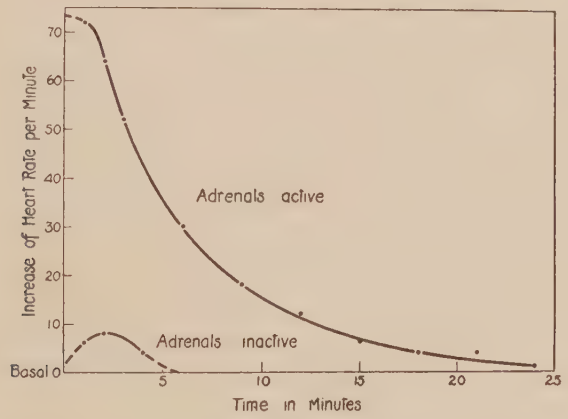


FIG. 47.—Adrenaline Secretion as a Result of Emotion.

Denervated heart preparation. Cat excited by barking dog for 2 minutes, then removed from cage and rested quietly on cushion. With adrenals inactivated there is only slight increase in heart rate, which rapidly subsides. With active adrenals there is a faster heart rate, which persists for over 20 minutes though cat was excited for only 1 minute. (Cannon and Britton, *Amer. Journ. Physiol.*, 1927.)

thetic fibres to the heart are extirpated and the cardiac fibres of the vagus are cut. In an animal treated in this manner *thyroxine*, some unknown substance which can be secreted by the *liver*, and *adrenaline* can still give rise to quickening of the heart. If the thyroid, liver, and adrenals are denervated, the heart rate remains remarkably steady under all conditions of the animal; if the nerves to the adrenals alone are left intact, any cardiac acceleration which may accompany any change in the state of the animal may be attributed to the secretion of adrenaline.

(*a*) In the presence of a barking dog, an increase in the rate of the denervated heart of about 20 beats per minute may be noted; if the animal becomes intensely excited and displays vigorous movement, the increase may be 30–80 beats per minute. After an exposure of 1 minute duration to a barking dog, the cardiac acceleration may persist for as long as 20 minutes (see Fig. 47). Slight movements, not associated with emotional disturb-

ance, or the act of walking cause an acceleration of 5–20 beats per minute. If the adrenal medulla is put out of action by removal of one gland and section of the nerves to the other, and the experiments repeated, variations in pulse rate not exceeding 5 per minute are obtained. The above observations illustrate that even trivial activity is accompanied by secretion of adrenaline, and that once secretion is set up it may long outlast the stimulus that gave rise to it (Cannon). The adrenaline thus poured out may be presumed to perform the following functions : (i) aid the redistribution of blood in the body (p. 128) ; (ii) increase the force and rate of the heart and the coronary blood flow, and thus enable the heart to cope better with the larger venous return ; (iii) mobilize liver glycogen and provide sugar for the active tissues ; (iv) diminish fatigue in skeletal muscle (p. 57) ; (v) possibly increase the red blood count and thus the oxygen-carrying power of the blood by stimulating the smooth muscle of the capsule of the spleen, and discharging the red cells stored in the interstices of the pulp : it is found that the spleen diminishes in size during very violent exercise even after it has been denervated. Relaxation of the bronchi (facilitating ventilation of the alveoli), dilatation of the pupil, closure of the sphincters, etc., may be other effects of value to the organism.

(*b*) Cramer has shown that exposure of a small animal overnight to cold causes disappearance of the granules of the cells of the medulla. This is interpreted as showing secretion of adrenaline as a result of the stimulus of cold, to the point of exhaustion of the gland ; but it is possible to suggest that cold arrested the formation of adrenaline. The denervated heart preparation, however, gives quite conclusive evidence : exposure of such an animal to a current of cold air increases the heart rate by 18–33 per cent. : if the experiment is repeated after inactivation of the adrenals the heart rate diminishes. Cold water in measured amounts may be introduced into the stomach ; as the body temperature must be kept constant, a " heat debt " is thus incurred, to discharge which increased heat production must take place ; thus the introduction of 200 c.cm. water at 10° C. into the stomach gives rise to a " heat debt " of about 1500 small calories per kg. In the denervated heart preparation such a procedure produces a marked initial acceleration, owing to the emotional disturbance set up by the passage of the stomach tube ; this then settles to a plateau level of about 25 per cent. above normal, and this persists for an *hour* or longer. Clearly, when the adrenals are intact, adrenaline is secreted under the circumstances of the experiment and presumably stimulates cellular metabolism and raises heat formation to the required level ; in addition, adrenaline constricts the skin vessels and so diminishes heat loss and mobilizes liver glycogen to provide fuel. With a " heat debt " up to 900 small calories per kg. the adrenaline reaction alone is sufficient ; shivering rarely occurs, or only lasts a few minutes. If the adrenals are inactivated the heart rate is unaffected or diminished by the introduction of cold water into the stomach ; but the same degree of " heat debt " now gives rise to shivering, which may go on for 17 minutes. In other words, adrenaline secretion is the primary reaction to cold ; shivering is the second compensatory mechanism. A bout of shivering may give rise to a sudden intense increase of the metabolism, *e.g.* to 60 or 80 per cent. above normal (Cannon) (see Fig. 48).

Addison's Disease.—The phenomena of *Addison's disease* remain to be

explained, and this is difficult in our present state of uncertainty. The cardinal symptoms of this disease are *weakness, low blood pressure, vomiting,* and *pigmentation.* It must be remembered that Addison's disease involves the whole of the adrenal, cortex as well as medulla, and, as a study of any series of pathological specimens shows, the upper group of abdominal ganglia are often involved in the fibro-caseous process. The weakness may be due to involvement of the adrenal cortex and to the tubercular disease of other viscera which is often present ; and also to lack of adrenaline, which retards the onset of fatigue in skeletal muscle. We know that involvement of the sympathetic ganglia is usually associated with vomiting. In the face of the

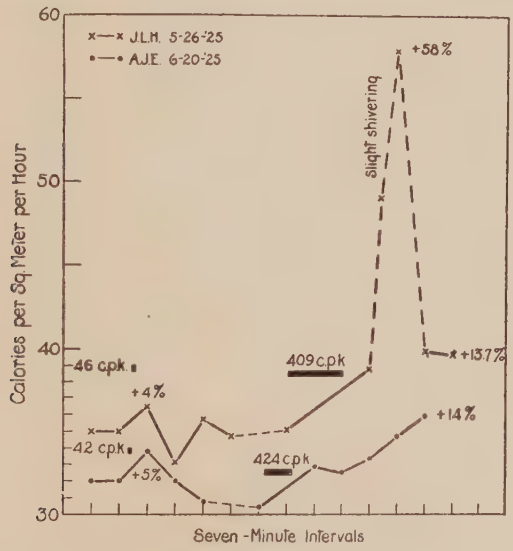


Fig. 48.—Effect of Cold on Metabolism.

J. L.H. took 520 c.cm. of water at 30°; this produces a "heat debt" of 46 sm. cal. per kg. and there is an increase of 4 per cent. in the metabolic rate. Later 354 c.cm. of water at 1° C. and 130 grm. ice ("heat debt" of 409 sm. cal. per kg.) increased the metabolism by 13·7 per cent.; a bout of shivering caused a sudden temporary increase of 58 per cent. in metabolism. A. J. E. ingested 420 c.cm. water at 30·2° (heat debt of 42 sm. cal. per kg.), which raised the metabolism by 5 per cent.; 260 c.cm. water at 1° C. and 139 grm. ice (heat debt of 424 sm. cal. per kg.) increased the metabolism gradually by 14 per cent. without shivering. (Cannon, Querido, Britton, and Bright, *Amer. Journ. Physiol.*, 1927.)

experimental evidence it is best to attribute the low blood pressure to the cutting off of the sympathetic vasomotor supply to the splanchnic area, or to the general asthenia. The basal metabolic rate is lowered (p. 126). Adrenaline is normally prepared by the adrenal medulla from tyrosine which is stored in the skin. If the medulla is destroyed, the mother substance, not being called upon, accumulates in the skin. A ferment known as tyrosinase then converts tyrosine into a pigmented body or melanin, which is deposited in the Malpighian layer of the skin. It must be admitted, however, that we are far from understanding the phenomena of Addison's disease.

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AFFERENT NEURONES OF INVOLUNTARY NERVOUS SYSTEM

We turn now to a more difficult part of our subject, namely, the arrangement of the *afferent neurones* of the involuntary nervous system. It is clear that animal experiments must be difficult to interpret, and there is little pathological evidence to assist us.

Anatomical studies show that the visceral afferents are chiefly medullated fibres of varying size with an admixture of a considerable number of unmyelinated fibres, all of which have their cell station in the posterior root ganglia or their cranial homologues. The great difficulty has been to determine which posterior nerve roots contain the afferents from any particular viscus. Clinical investigations of the regions of referred pain (*vide infra*) and tenderness in visceral disease have been of great value. We quote the results of such researches in the form of a table which is slightly modified from Head's paper. It will be noted how closely the afferent inflow resembles the arrangement of the efferent outflow already described. Here, too, no reception by the spinal cord occurs between L2 and S2 nor in the lower cervical region.

Organ.	Areas of Referred Pain and Tenderness.
Heart	Th1, 2, 3. Some cervical nerves (vagus).
Lungs	Th1–5. Cervical nerves (vagus).
Stomach	Th6–9. Cardiac end, Th6, 7. Pyloric end, Th9.
Intestine to colon	Th9–12.
Rectum	S2–4.
Liver and gall-bladder	Th7–10, (?) 6. Cervical nerves (? vagus).
Kidney and ureter	Th10, 11, 12. Kidney, chiefly Th10. Ureter, L1.
Bladder	Th12, L1, 2.
Prostate	Th10, 11.
Testis Ovary	Th10.
Uterus (in contraction)	L1, Th10–12.
Appendages	Th11–12, L1.

Visceral Sensibility.—The viscera themselves are completely insensitive to the stimuli which produce pain in the outer body wall. Thus after the peritoneal cavity is opened, the abdominal viscera can be operated on in the conscious subject without producing pain. In the second stage of a colotomy operation the extruded portion of the large bowel is incised to make a permanent opening, and the conscious patient feels nothing. Hunter

demonstrated that the viscera could be cut and burnt while the animal ate its food unconcernedly.

The serous membranes generally are quite insensitive. We have already noted that the visceral peritoneum can be incised painlessly. Much confusion exists concerning the sensitiveness of the parietal peritoneum. It appears that the loose connective tissue *outside* the parietal peritoneum is richly endowed with nerve endings and fibres (which are derived from the nerve supply of the muscles of the abdominal wall), and is exquisitely sensitive. No nerve fibres, it is said, can be traced to the peritoneum itself.

Speaking generally, the viscera are completely insensitive to temperature stimuli. In the œsophagus, stomach, and rectum, however, it is probable that extremes of heat and cold may be dimly appreciated, *i.e.* protopathic temperature sensibility may be present. The hollow viscera are sensitive to changes in the *tension* of their muscle coat. In the case of a few of the viscera the sensation is referred to the organ itself; in most cases it appears to come from the body wall. If a balloon is introduced into the œsophagus and then inflated, a sensation of fullness is felt, situated deeply beneath the sternum in the middle line; the level at which the balloon lies is located with fair accuracy. Similar accuracy of localization is present in many cases of carcinoma of the œsophagus. In about 20 per cent. of the cases the feeling of obstruction is in the upper third of the œsophagus, although the stenosis is really in the lower third; a state of spasm is then found to be present in this part of the œsophagus. If the stomach is distended with air the sensation of fullness is felt deeply beneath the upper part of the anterior abdominal wall in the middle line. The kidney and the testis appear to be sensitive to external pressure. When a movable kidney is palpated bimanually an aching pain is felt locally; on pressing the testis, pain is in this case, too, first localized over the point of pressure. Branches from the genital branch of the genito-crural have been traced to the visceral layer of the tunica vaginalis, and it is possible that impulses which pass up these somatic fibres may arouse the pain described.

When violent *pressure* changes occur in a hollow viscus, pain is experienced which may be extremely severe in character. The pain, however, is not usually felt in the viscus affected, but is referred to some definite area on the surface of the body (except perhaps in the case of the stomach and œsophagus, in which it is claimed that visceral pain can be experienced). A simple example may be quoted. If the bowel is distended with a large warm water enema, strong peristaltic waves are set up and great pain is experienced. The pain is not referred to the rectum, but to the middle line above the pubis. Similarly, Mackenzie observed that when peristaltic waves passed over an exposed loop of intestine during an operation on a conscious subject, the patient groaned and complained of pain—not in the contracted intestine, but in the region of the umbilicus. It is not clear whether powerful peristaltic waves alone give rise to pain, or whether excessive stretching of the hollow viscus is adequate too. As a rule, of course, the two phenomena are associated together.

It is not clearly understood why the pain is not felt in the affected viscus. If the patient is questioned casually, he may complain of pain in his "heart," or "stomach," or "bowel." But the patient's knowledge of the anatomy of the parts is most vague, and close investigation reveals that the pain is felt

in some part of the body wall. This phenomenon is known as *referred pain*, and its mode of production is not easy to explain. The cortex is normally unaccustomed to receive impulses from the viscera, and so when a particularly powerful sensory stimulus is received the brain projects it to the body wall from which it usually receives impulses. Head suggests that this is an example of a general law ; when a painful stimulus is applied to a part of low sensibility in close central connection with a part of much greater sensibility, the pain produced is felt in the part of higher sensibility. In tabes, for example, a pin-prick applied to a skin area of low sensibility is referred to an adjacent skin area of greater sensibility. (This phenomenon is called *allocheiria*.) If the impulses from a viscus enter a certain posterior nerve root, the pain is referred to the skin area supplied by that particular posterior nerve root. The heart, for example, sends its afferents into the posterior nerve roots of Th1, 2, 3, and so the pain of heart disease is frequently referred to the inner side of the arm and the front of the chest. Mackenzie calls referred pain a *viscero-sensory* reflex, *i.e.* the pain from the viscus is reflected to a certain area of the body surface. It is found that the regions of referred pain are fairly constant for any given organ, and in that way the segments of the cord receiving the afferent impulses from any viscus have been worked out. The results of such investigations have already been shown in the Table on p. 134. Many points of detail remain unexplained. The referred pain does not necessarily involve the *whole* of any segment, and as a rule there are certain special regions in the segment to which pain is referred. From the stomach, small and large intestine, the pain is felt in the *middle* line ; in the case of the other hollow viscera—*e.g.* the gall ducts and ureter—it is referred to the affected side. Accurate knowledge of the sites of referred pain from the various internal organs is of the greatest help in diagnosing the site of a lesion ; but more research on this subject is still needed.

Disease of the parenchyma of *solid* organs produces no very definite sensory symptoms. Thus tuberculosis of the lungs, advanced nephritis, or cancer of the liver may be quite painless diseases. The tender liver of heart disease may result from nervous impulses set up in the stretched capsule of the organ. Consciousness of the heart's action is sometimes present and is called " palpitation."

If abnormal impulses constantly enter a certain region of the spinal cord, it becomes an " *irritable focus* " (Mackenzie), *i.e.* it becomes modified in some unknown way so that the intensity of any impulses entering it becomes increased. Stimuli applied to the sensitive layers of the body surface which would normally only arouse slight discomfort, now become endowed with distinctly painful properties—*i.e. hyperalgesia* is present in the corresponding segments of the body wall. It may involve the skin, the muscles, and other structures.

i. *Cutaneous hyperalgesia* due to visceral disease may be superficial or deep. The former is recognized by the extreme sensitiveness of the skin when lightly stroked with a pin-head or when moving the hairs ; the latter, when pressure is made on the whole thickness of the skin between finger and thumb. The deep form is commoner than the superficial, and always accompanies it. The borders of the area of hyperalgesia are ill defined and variable (Mackenzie). In these areas the superficial reflexes (*e.g.* the abdominal) are exaggerated.

ii. *Muscular hyperalgesia* is more common, and can be best elicited by grasping the edge of the muscle, especially in the case of trapezius, sterno-mastoid, or rectus abdominis. This muscular hyperalgesia is worse after exercise.

iii. Mackenzie noted tenderness over the *vertebral spines* in certain cases of visceral disease. The affected spines were : affections of the heart Th1–4, stomach Th4–8, liver Th8–11, rectum and uterus L5, S1, 2.

Pain is referred to the *testis* in renal colic because the tunica vaginalis has the same segmental somatic supply (L1) as the visceral supply of the ureter. The scrotum, which is supplied by the sacral cord, is not tender.

Besides these sensory phenomena *viscero-motor* reflexes may be set up by visceral disease. In response to visceral impulses corresponding groups of muscles harden. In the case of the flat muscles of the abdominal wall the contraction may involve one segment only of a muscle. The contraction is long lasting and may persist for days or months. It is readily evoked by palpation. When chloroform is administered, these regions are the last part of the musculature to relax and may remain stiff even in the deepest stage of anæsthesia. Even when cut through the affected muscle may remain stiff and unyielding and even hamper operative procedures. These facts suggest that one is dealing here with a postural reflex.

Other *viscera* may be reflexly affected too. Thus *viscero-secretory* reflexes may be recognized, as in cases of angina pectoris, where saliva may dribble from the mouth.

To summarize : abnormal impulses from viscera may result in—

i. Referred pain (viscero-sensory reflex).

ii. Tenderness, *e.g.* cutaneous and muscular hyperalgesia, tender spines (? facilitated conductivity).

iii. Muscular contraction (viscero-motor reflex).

iv. Glandular activity (viscero-secretory reflex).

An analysis of the symptoms of *angina pectoris* makes these principles clearer (Mackenzie). It is likely that the syndrome of angina may be produced by one of several conditions, but it has been conclusively proved that in a proportion of the cases it is the result of occlusion of a branch of one of the coronary arteries by *thrombosis* (p. 244). In this latter condition, the pain, which is agonizing in character and may last for hours or even days, is not complained of in the heart itself. The afferents from the heart pass into Th1–3 and up the vagus nerve. For some unknown reason, impulses up the vagus are referred to the cervical segments (chiefly C2, 3, 4).

The symptoms are thus explained by Mackenzie :

i. Referred pain (viscero-sensory reflex) may, for example, be experienced over the outer part of the left side of the chest (Th1, 2, 3), down the inside of the arm (Th1), up the neck to the angle of jaws (C3, 4), and in both shoulders and back ; the pain is often referred to the epigastrium, and may simulate that of an abdominal catastrophe and give rise to vomiting. A striking feature of coronary thrombosis is the very wide area involved by the referred pain.

ii. Tenderness is present over these regions too.

iii. Characteristic of the disease is a sense of constriction as though the chest were gripped in a vice, or as if the breast bone would break. Mackenzie attributes this to a viscero-motor reflex, *i.e.* reflex spasm of the intercostal muscles, which prevents movements of the chest.

iv. The abundant flow of saliva or polyuria is evidence of a viscero-secretory reflex.

Visceral Reflexes.—Under normal conditions of health, we receive no conscious sensations from most of our viscera. The bladder and the rectum are exceptions to this rule, because at various intervals we receive information concerning the state of tension in these organs.

The afferent impulses passing in from the viscera are chiefly expended in reflexly affecting the activity of various involuntary structures like smooth muscle or glands. We will mention examples from some of the more important reflexes associated with the chief systems of the body, both in health and in disease conditions:

1. Respiratory Reflexes.—Afferent impulses from the lungs pass in the *vagus* nerve, and also in the posterior roots of Th1–5, chiefly Th2, 3 (Möllgaard). The vagal fibres proceed to the respiratory centre and regulate the rhythm of the respiratory movements (p. 328).

Stimulation of the nerve endings in the lungs by irritant gases produces marked reflex changes. There is first a prolonged deep expiration, followed by a short period of apnœa and then by rapid respiration. This appears to be a reflex in which the afferents travel *via* the sympathetic to the dorsal cord (Roger).

Irritation of the *pleura* reflexly produces coughing, but no pain sensibility is present in the pleura. This statement seems greatly at variance with the well-known severe pain of pleural inflammation. Neither scraping nor penetration of the parietal or visceral pleura produces pain, as can be well shown when resections of ribs are carried out under local anæsthesia.[1] The nerve supply of the pleura is not known; cerebro-spinal nerve fibres do not appear to have been traced into it, nor do nerve plexuses lie in the surrounding connective tissue. Mackenzie suggests that the pleura receives visceral afferent fibres, and that in pleurisy reflex spasm of the corresponding intercostal muscles occurs, analogous to the hard abdominal wall of peritonitis. The spasm of the muscles hinders the movements of the chest, which consequently are constrained and limited. The muscles are hyperalgesic, and when they are used in breathing pain is aroused. The symptoms are very similar to those found in primary involvement of the muscles in "muscular rheumatism," and it is well known that the differential diagnosis may be difficult.

2. Cardiac Reflexes.—The afferents from the heart pass in the vagus nerve to the medulla, and probably also into the posterior nerve roots of Th1–3. These afferents come from both the arterial and venous ends of the heart:

(1) From the left ventricle and the root of the aorta impulses pass up the depressor nerve, reflexly inhibiting the vasomotor centre (and lowering the blood pressure), and stimulating the cardio-inhibitory centre and slowing the heart (p. 257).

(2) From the right auricle and the root of the great veins impulses pass in the vagus nerve and reflexly accelerate the heart (p. 258).

[1] This operation is, however, usually performed for diseases affecting the pleura, and the insensitivity may be secondary to the local pathological process. Some observers find that healthy subjects complain of pain as soon as an exploring needle penetrates the pleura.

The remarkable reflex effects resulting from abnormal stimuli from the heart in angina pectoris have already been discussed (p. 137). It may be mentioned that McDonnel, in a case with a lax abdominal wall, was able to palpate the under-surface of the auricles, and to demonstrate that pressure on the auricles gave rise to symptoms resembling those of angina.

The heart may be affected reflexly from other viscera. Thus during periods of strong hunger contractions the rate of the heart is increased. Again, dilatation of the stomach by means of a balloon produces the same effects. It is obvious that the stomach in heart disease may not only embarrass the organ mechanically, but may disturb its action reflexly. Irritant vapours stimulating afferent nerve endings in the lungs reflexly slow the heart. It has recently been shown [1] in operations on patients with pericardial effusion that both the visceral and parietal layers of the *pericardium* are insensitive to pain; this seems to explain the fact that many cases of pericarditis pursue a painless course. The pain that is undoubtedly noted in some patients may be due to involvement of the mediastinal connective tissue or to the primary condition, *e.g.* coronary thrombosis.

Local Nervous Reflexes.—Of recent years greater attention has been devoted to the local nervous plexuses in the abdomen, and it is thought that much correlation between the abdominal viscera is effected by means of these plexuses. The control of the cardiac and pyloric sphincters of the stomach may depend in part on local reflex arcs. It has been suggested that the secretion of gastric juice in response to certain chemical substances in the stomach, may be an example of such a mechanism (p. 383).

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MICTURITION

WE will briefly recapitulate the essential facts about the nerve supply of the bladder. The *efferent* fibres pass by way of—

1. The sympathetic: the connector cells lie in L1, 2; the connector fibres pass in the inferior splanchnic nerves to the inferior mesenteric ganglia. The excitor fibres arise here and pass in the hypogastric nerves to the bladder.

2. The sacral autonomic: the connector cells lie in S2, 3; the connector fibres are found in the nervi erigentes and end in excitor cells on the bladder wall—forming the pelvic plexus. The excitor fibres pass direct to the muscle of the bladder.

The sympathetic relaxes the detrusor and closes the sphincter vesicæ; the sacral autonomic has the antagonistic effect—it stimulates the detrusor and relaxes the sphincter.

The *afferent* fibres from the bladder have been shown (Riddoch) to pass

[1] Capps, *Arch. Int. Med.*, 1927, vol. xl. p. 715.

up the hypogastric nerves, through the inferior mesenteric ganglia, inferior splanchnic nerves, lateral sympathetic chain, white rami, and into the posterior nerve roots of Th12, L1 and 2. The cell stations for these afferent fibres lie, of course, in the corresponding posterior root ganglia. It is found that after destruction of the sacral posterior nerve roots the penis is anæsthetic, and the passage of a catheter along it fails to elicit any response. But as soon as the point of the instrument penetrates the bladder in the region of the trigone, the patient recognizes that something has happened, *i.e.* bladder sensibility is present. He is also aware if the bladder is full, and gets increasing discomfort as the distension becomes greater. It is worth noting that the pain is referred to the region of the pubis and groins, *i.e.* in the distribution of Th12, L1. The loss of bladder sensation which occurs in tabes is probably due to the lesion affecting the lumbar posterior nerve roots—a favourite site for the syphilitic toxin (cf. p. 40).

Division of the spinal cord at the level of the eleventh thoracic segment completely abolishes vesical sensibility.

Cortical Control.—The path of the afferent fibres within the central nervous system is not clearly known. Attempts have been made to define a higher centre for control of the bladder in the motor area, and in the upper

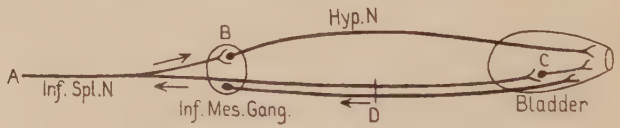

FIG. 49.—Diagram of Axon-Reflex in Bladder.

Inf.Spl.N. = Inferior splanchnic nerve ; Hyp.N. = Hypogastric nerve ; Inf.Mes.Gang. = Inferior mesenteric ganglion. (See text.)

part of the post-central gyrus. The path in the spinal cord for the motor fibres from the cortex lies in the vicinity of the pyramidal tracts in the dorsal part of the lateral columns.

The Bladder Axon-Reflex.—A curious experiment of Sokownin must be described, though whether it has any bearing on the normal mode of working of the bladder is uncertain. The inferior mesenteric ganglia are isolated from the spinal cord by dividing the inferior splanchnic nerves. One hypogastric nerve is cut and its central end is stimulated. Contraction of the trigone of the bladder occurs, associated with pallor of the rectum and contraction of the sphincter vesicæ. Clearly the efferent arc of this reflex must involve motor fibres in the opposite hypogastric nerve. It is obviously not a reflex through the cord, because, as stated, the connections with the cord were severed. If time is allowed for the inferior splanchnics to degenerate, the reflex can no longer be elicited. It is suggested that this is not a true reflex, but depends entirely on the fibres of the inferior splanchnics. In the diagram (Fig. 49), the connector fibre A is supposed to give a collateral to a cell B in the opposite inferior mesenteric ganglion, and to continue down its own hypogastric nerve to the bladder, to end round a cell (C). Stimulation of the central cut end at D results in the impulse passing up the fibre to the bifurcation of the axon, and then down the collateral to the opposite side of the ganglion, to be relayed from the cell B to the opposite half of the

bladder. This is another example of an "axon reflex" (cf. p. 35), *i.e.* a reflex depending on the bifurcation of an axon. We do not know whether such a bladder reflex occurs normally in the body.

Postural Activity in the Bladder.—The bladder is an organ in which the phenomena of tone have been extensively studied, and our information concerning it is fairly complete. If a dead bladder is examined—say twenty-four hours after death—and fluid is injected into it, it is found that at first no rise of internal pressure takes place. The fluid serves first of all to straighten all the folds that are present. Then, as more fluid is pumped into the bladder, the pressure within it rises with increasing rapidity for every fresh rise in bladder content. On reaching the limit of elasticity of the bladder wall the gradient of ascending internal pressure becomes very steep prior to the final bursting of the organ. These observations illustrate the behaviour of the dead bladder and contrast markedly with the response of the living organ. Mosso and Pellacani passed a catheter into the human bladder in normal subjects and measured the internal pressure under a variety of conditions. To their surprise they found little evidence of zero pressures even in the apparently "empty" bladder. The pressure usually ranged round 15 cm. of water and seemed to be quite independent (within limits) of the volume of fluid in the bladder. If more water was pumped in, the pressure rose momentarily but soon fell once more to its original level; and similarly, if some water was allowed to escape through the catheter, the bladder pressure fell for a short time and then rapidly readjusted itself. The bladder wall therefore adapts itself to its contents in such a fashion that the internal pressure is always about the same. We can imagine that as urine enters from the ureters the bladder fibres actively elongate, increase the capacity of the bladder, and so prevent any rise of internal pressure. In the same way, after the bladder has apparently emptied itself, its fibres remain shortened so as to grip the minute amount of residual urine as firmly as they did the larger quantities previously present. The living bladder thus "enfolds its contents with the same light grip," whether they be ample or little, in the same way as the hand can grasp a ball with the same light clasp, whether the ball be large or small. The posture of the bladder is always adapted to maintain the same tension, with varying volumes of urine. The general characters of muscle acting posturally (cf. p. 54) are here exemplified—the very low energy consumption, the unfatiguability, and the lack of relationship between tension and length of muscle fibre. To complete the analogy with skeletal muscle, the bladder at times executes movements: *i.e.* when micturition takes place.

These remarks apply to the detrusor muscle. The sphincter muscle, too, maintains an attitude or possesses tone, but its function is to maintain a constant position and keep the bladder closed, except, of course, during micturition, when its tonic activity is temporarily inhibited.

It appears that postural activity (tone) in smooth muscle is not so completely dependent on reflex nervous impulses as tone in voluntary muscle. A certain power of adaptation which is independent of the nervous system appears to be present. But under normal conditions this adaptation of the bladder to its increasing contents is probably carried out reflexly; afferent impulses pass to the spinal cord and efferent sympathetic fibres from the lumbar segments cause the bladder wall to relax (and thus lower the internal

pressure) and reinforce the closure of the sphincter. Up to a certain point the spinal cord possesses the power of regulating the behaviour of the bladder without consulting the higher centres. Should the bladder contents exceed this limit—and this limit will vary with many conditions—the cord has no further powers assigned it, and so the pressure in the bladder will begin to rise as its muscle fibres are increasingly stretched. When the pressure reaches 18 cm. of water, afferent impulses reach the higher centres and are translated into a "desire to micturate." Probably rhythmic contractions occur in the bladder and these may set up reinforcing afferent stimuli. In civilized society the further sequence of events depends on circumstances. If it is inconvenient to micturate, impulses from the cerebral cortex act through the sympathetic nerves and further relax the bladder wall. As the capacity of the organ is increased, the internal pressure falls. The afferent impulses cease and the desire to micturate temporarily passes off. By constant practice, the bladder may become accustomed to accommodate very large quantities of urine before its fibres fail to relax and allow a rise of intravesical pressure to take place. Many women and persons engaged in sedentary occupations can hold their water for very long periods without discomfort.

Voluntary Micturition.—On the other hand, the bladder may be voluntarily emptied in response to the "desire to micturate." Impulses from the cortex then pass down to the sacral segments and along the nervi erigentes to stimulate the bladder wall and to relax the sphincter. Certain accessory muscles are also involved: the abdominal wall contracts, the diaphragm descends and the breath is held with the glottis closed. The rise of intra-abdominal pressure which results compresses the bladder from without. The intravesical pressure rises to 20 or 30 cm. of water and the bladder is evacuated.

Micturition can also be carried out voluntarily before urgent afferent impulses have been received.

In young *children* the process is different. Postural activity in the bladder is less perfect, and so quite small quantities of urine may raise the pressure adequately to send up afferent impulses to the cord. The higher centres are not consulted at all and micturition occurs entirely reflexly from stimulation of the nervi erigentes.

The postural behaviour of the bladder can be influenced by a variety of circumstances. In certain forms of emotional stress, as in the anxious moments preceding an examination, the power of the bladder to elongate its fibres as its contents increase, appears to be in abeyance. The well-known result is that there is a constant desire to micturate with the passage of but small quantities of urine on each occasion. Frequency is produced in a similar way when the bladder wall (or mucous membrane) is irritated by inflammation or stone. The nature of the disturbance in the so-called "enuresis of children" is not clear. Many authorities believe the trouble is psychical and that it is analogous to the "emotional" frequency described above.

According to Mackenzie, frequency may be present as a "referred" phenomenon. Just as sensory impulses from a viscus are often referred to corresponding segments of the skin, so may they be referred to other *viscera* innervated by the same spinal segments. In cases of appendicitis, frequency of micturition may occur without any adhesions to the bladder *necessarily*

being present. Impulses from the appendix are referred as coming from the bladder (which has a similar segmental innervation because the bladder is an organ impulses from which have an easier access to consciousness).

We must now discuss the effects on micturition of injuries to the spinal cord.

Acute Trans-section of the Cord.—If the spinal cord is completely trans-sected by some acutely acting injury, voluntary micturition is completely abolished. The activity of the detrusor muscle remains in abeyance for a long period, but sphincter tone returns very soon. Retention of urine is therefore complete from an early stage. If no catheter is passed, the bladder becomes increasingly overstretched. The sphincter is finally forced open by the high intravesical pressure and small quantities of urine escape at frequent intervals—a condition of "retention with overflow." Owing to the excessive stretching of the bladder wall, its nutrition suffers and it becomes very prone to infection. Cystitis may occur, and death results from the usual complications of ascending urinary infection. If the inflammation is of a lower grade, the bladder shrinks and the musculature is so damaged in consequence that it becomes incapable of ever again responding normally to internal stimuli; it contracts at irregular intervals and evacuates small amounts of urine.

If the bladder is catheterized within twenty-four hours of the spinal injury, fitful evacuation of urine may occur at intervals, but most of the urine has to be drawn off. In the course of time, however, reflex micturition becomes more perfectly established. The amount of urine present in the bladder before reflex evacuation occurs shows wide individual variations. By taking a deep breath, a bladder which usually empties at a content of 380 c.cm. may empty when it contains but 80 c.cm. Similar results follow when the flexor reflex is elicited or the glans penis is stimulated. In the cases where the "mass reflex" is obtained, evacuation of the bladder may occur at the same time. Reflex evacuation can often be obtained when a catheter is in position, though it may be impossible otherwise. Presumably in such cases the co-ordinated inhibition of the sphincter has not yet been established, and the detrusor muscle is unable to overcome the resistant sphincter.

When the functional activity of the isolated region of the spinal cord becomes depressed through toxæmia, reflex bladder activity passes off in the reverse order in which it has returned—the detrusor weakens first (with retention and overflow), and finally sphincter tone is lost, and dribbling results. A similar state of affairs obtains in any extensive destruction or inflammation of the distal end of the spinal cord.

Other Spinal Lesions.—(*a*) In patients in whom the lumbar region of the cord is injured, the sphincter vesicæ becomes atonic and dribbling results without previous accumulation of urine in the bladder. This may be termed "*paralytic incontinence.*"

(*b*) If the cauda equina or the sacral posterior nerve roots are destroyed, bladder sensibility persists. Although in the former case the motor centre for the detrusor muscle is cut off from the bladder, the organ can still empty itself automatically. It appears that the isolated bladder, if it be otherwise healthy, will respond to internal stretching by co-ordinated evacuation.

(*c*) The afferent impulses from the bladder may be lost or diminished from

lesions of the lumbar posterior nerve roots, as in tabes. Knowledge of the state of distension of the bladder is absent. Micturition can still occur when the patient wishes it; but if he does not attend to this at regular intervals, the accumulation of urine precipitates involuntary automatic evacuation (cf. *b*) ; or else the pressure in the bladder may rise till the resistance of the sphincter is overcome and dribbling occurs.

(*d*) Efferent control of the bladder is disturbed in lesions of the pyramidal tracts, in the vicinity of which the fibres for the voluntary regulation of the bladder are found. The patient is completely conscious both of the state of his bladder and of all events occurring in his bladder. Voluntary control of micturition is interfered with. The patient has difficulty in initiating the act and, further, he cannot hold his water at will : no sooner does the desire come on than he must respond to it immediately. In other words, his voluntary control of both motor and inhibitory fibres to the bladder is impaired. Such symptoms occur in any spinal lesions involving both pyramidal tracts—*e.g.* disseminated sclerosis, early compression of the cord, syringomyelia, etc.

Obstruction to the outflow of urine from the bladder may be due to anatomical obstacles (*e.g.* enlarged prostate or urethral stricture) or to functional derangements (*e.g.* a tonic sphincter with a relatively weak detrusor) ; retention of urine consequently tends to occur, and the intravesical pressure rises till it causes expulsion of the urine. When the obstruction is mechanical, the stretching of the bladder wall acts at first as a growth stimulus resulting in hypertrophy of its fibres and increase in their expulsive powers ; this for a time enables the obstacle to be overcome. But if the bladder is overstretched its wall becomes paralysed and normal evacuation no longer takes place. At first small rhythmical contractions may occur and may account for some dribbling, but the escape of urine is chiefly due to overflow from the overfilled organ. This is referred to as retention with overflow or "*passive incontinence.*"

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III

THE DUCTLESS GLANDS

Pituitary body—Structure—Action of posterior lobe extracts ("pituitrin")—Functions of pars intermedia—Diabetes insipidus—Pars anterior—Acromegaly, gigantism—Hypopituitarism—Active principle—Relation of hypothalamus to pituitary.

Thyroid—Structure—Extirpation—Myxœdema—Cretinism—Simple goitre—Thyroxine—Hyperthyroidism—Summary.

Parathyroid—Extirpation—Tetany—Parathyroid hormone—Hypercalcæmia—Toxic theory—Tetany in man—Causes—Blood changes.

Testis—Structure—Extirpation—Tying vas—Cryptorchidism—Grafting—Interrelations.

Ovary—Structure—Menstruation and the œstrous cycle—Extirpation—Cryptorchidism—Grafting—Feminizing experiments—Ovarian hormone—Preparation and Standardization—Functions of ovary during pregnancy—Summary.

Structure of mammary gland—Secretion of milk—Composition—Origin of constituents—Conditions affecting it—Thymus—Structure—Extirpation—Hyperplasia—Status thymo-lymphaticus.

THE PITUITARY BODY [HYPOPHYSIS]

The anatomical relations of the different parts of the pituitary body and the adjacent region and their development are illustrated in Fig. 50 and summarized in the following table :

		Development.
Anterior lobe	Pars anterior	Rathke's pouch from stomodæum.
	Pars tuberalis	
Posterior lobe	Pars intermedia	
	Pars nervosa	
Infundibulum (stalk)		Floor of third ventricle.
Tuber cinereum		

The *pars anterior* is large, compact, and highly vascular ; it consists of cells arranged in nests or columns surrounded by connective tissue. The cells are of two kinds : (1) *chromophobe*, without affinity for dyes ; (ii) *chromaphil*, which stain readily and are subdivided according to the character of their granules into α and β cells : α (*eosinophil*) cells stain with eosin, acid fuchsin ; β (*basophil*) cells stain with hæmatoxylin. Innocent tumours (adenoma) arise clinically from both kinds of cells : tumours consisting of the chromophobe cells are associated with signs of hypopituitarism ; in acromegaly tumours of the α (eosinophil) cells are almost constantly present. Tumours made up of basophil cells alone are rare. In complex derangements of pituitary function (dyspituitarism) adenomata consisting of both kinds of cells are found. The functional significance and mutual relation of the different kinds of cells is obscure.

The *pars tuberalis* consists of numerous vesicles lined by basophil cells ;

the vesicles contain coagulated fluid and cellular elements which are probably derived from the degeneration of the surrounding cells.

The *pars intermedia* is thin, poorly vascularized, and formed of densely packed basophil cells. Cysts or vesicles containing colloid are described in this region; it is believed by most workers that they are normal structures and contain the active physiological principle of the pars intermedia.[1]

The *pars nervosa* consists mainly of neuroglial elements and is highly vascular. "Hyaline" or "colloid" masses can often be found here; it

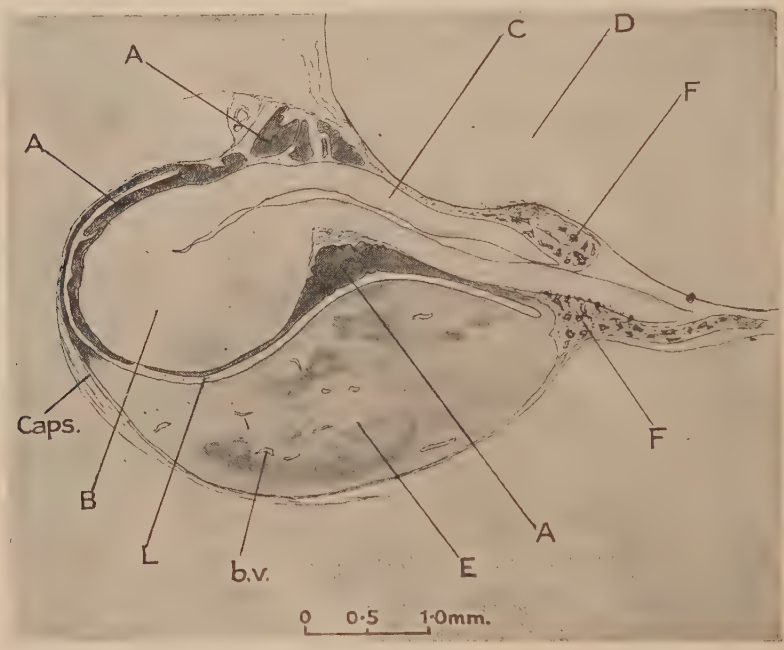


FIG. 50.—Pituitary of Cat.

A=Pars intermedia; B=Pars nervosa (neuralis); C=Stalk (infundibulum); D=Hypothalamus; E=Pars anterior; F=Pars tuberalis; L=cleft (residual lumen of Rathke's pouch); Caps.=capsule; *b.v.*=blood capillary (Woodger).—From SWALE VINCENT.[2]

is suggested that they represent the secretion of the pars intermedia which enters the nervosa either to be absorbed into its blood vessels or to enter the cerebro-spinal fluid of the third ventricle (*v. inf.*).

Functions of the Pituitary Gland. The pars *anterior* forms an internal secretion, which is related to skeletal growth, to mental development, and to the development of the sex glands.

The pars *intermedia* manufactures one or more principles known as

[1] According to de Beer the vesicles are rarely present and are to be regarded as a form of pathological degeneration.

[2] Figs 50, 54, and 87 are reproduced from Swale Vincent, *Internal Secretion and Ductless Glands*, by permission of the author and Messrs. E. Arnold.

"*pituitrin*."[1] Its rôle in the body is not certain, but it possibly influences metabolism, controls the flow of urine, and regulates capillary tone. The pars *nervosa* is a vehicle for the transmission of the secretion formed by the intermedia, into the blood or cerebro-spinal fluid. Extracts of pars nervosa yield pituitrin, but it is scarcely conceivable that an entirely non-glandular tissue like this should manufacture a secretion. The functions of the pars *tuberalis* are not known.

Action of Posterior Lobe Extracts ("Pituitrin").—Pituitrin stimulates unstriped muscle extensively throughout the body. Its action is quite independent of the condition of the nerve supply, whether it be destroyed or left intact. The effects of injecting pituitrin are as follows:

(*a*) Circulation.—(i) The *rate* of the heart is usually diminished; this is less evident after section of the vagi. The *force* of the heart may be slightly increased, but in some species (rabbit) it is diminished. The arterioles are contracted and the blood pressure rises considerably. The rise of pressure takes place relatively slowly; it is maintained for a long time, and then falls gradually. Crude extracts of posterior lobe are contaminated with a depressor substance which is probably *histamine* (this can be removed by prolonged treatment with absolute alcohol); a second injection of unpurified extracts produces a fall of the blood pressure, and this happens after any subsequent injection during the next two hours. Probably the body becomes immune to the pressor principle, but still reacts to the depressor impurity (histamine).

(ii) Pituitrin has an extremely important action on the *capillaries*, causing them to contract. (See p. 292.)

(iii) In the *human* subject subcutaneous injection of the usual doses of pituitrin (0·5 to 1 c.cm.) produces no very definite effects on the blood pressure. The pressure may rise slightly, or fall a little, or remain quite unaffected. With subcutaneous injections, local pallor of the skin results from local capillary constriction. With intramuscular injections marked pallor of the skin occurs (especially that of the face) from generalized capillary constriction.

(*b*) The Kidney.—(i) Pituitrin in the anæsthetized animal causes the renal vessels to dilate as shown by the increased volume of the kidney. Because of the greater blood flow and the rise of blood pressure, the amount of the urine formed is augmented.

(ii) It is important to note that there is considerable discrepancy between the action of pituitrin in the anæsthetized cat and its effects in the unanæsthetized animal or in man. It is generally agreed that the injection of pituitrin *diminishes* the flow of urine in man.

(iii) Furthermore, it will delay for four or five hours the diuresis which normally follows on ingestion of large quantities of fluid. (Cf. Fig. 108, C, p. 469.)

(iv) The isolated kidney, when perfused with blood from a heart-lung preparation, secretes an extremely dilute urine. If the pressure and quantity of the blood passing through the kidney are kept constant, the addition of low concentrations of pituitrin results in the passage of a smaller volume of more concentrated urine; this is accompanied by *increased oxygen*

[1] It must be clearly noted that "pituitrin" is merely the proprietary name of a commercial extract of the posterior lobe of the pituitary body; it is used in the text in the sense of "extract of posterior lobe."

consumption by the kidney. These results suggest that the "anti-diuretic" action of pituitrin is not due to the vascular changes that it may produce in the kidney; it probably stimulates the epithelium of the renal tubules to absorb more water and thus concentrate the urine. According to Verney, if the blood from the heart-lung preparation is first sent through the *head* of the animal it also exerts an "anti-diuretic" action on the kidney, probably owing to having absorbed pituitrin during its passage through the gland.

(*c*) The Uterus.—The uterus of the virgin guinea-pig suspended in oxygenated Ringer's solution is made to contract. This method is employed for assaying preparations of pituitrin.

Pituitrin has no effect on the virgin human uterus, nor on the pregnant uterus. During labour, however, and more especially during the latter part of the second stage, it powerfully increases the uterine contractions, and thus helps to expel the fœtus, and, later, the placenta. It is stated that, if for any purpose it is found necessary to induce abortion, pituitrin administered for some days previously will facilitate the subsequent mechanical emptying of the uterus.

(*d*) Other Organs.—The smooth muscle of the bladder and of the small and large intestine are stimulated. The strands of plain muscle which lie between the alveoli of the mammary gland are contracted, and thus any preformed milk can be squeezed out. Pituitrin is not a galactagogue; it does not increase the amount of milk formed, but merely expresses the milk already present in the breast. The action on bronchial muscle is still in dispute; probably it is relaxed, and so pituitrin may be beneficial in asthma.

(*e*) Carbohydrate Metabolism.—Pituitrin usually produces a transient rise of the blood sugar, and may possibly induce glycosuria. It antagonizes the action of the internal secretion of the pancreas—insulin. Thus, if pituitrin and insulin are injected simultaneously, in suitable proportions, the pituitrin diminishes or abolishes the fall of the blood sugar which is usually produced by the insulin (Burn). If insulin be given in large enough doses to produce convulsions and hypoglycæmia in a normal animal, an injection of pituitrin causes a rapid rise of the blood sugar, and will stop the convulsions. The explanation of these results is uncertain—pituitrin may convert the glycogen of the liver into glucose.

It has recently been shown that posterior lobe extracts contain at least two active principles[1]: (i) *oxytocin*, which stimulates the uterus but has negligible pressor action; (ii) *vasopressin*, which has the pressor, anti-diuretic, and probably the intestine-stimulating actions. (Aldrich.)

Pituitrin in the Cerebro-Spinal Fluid. Pituitrin has been demonstrated in the cerebro-spinal fluid of man and animals by the use of the isolated virgin guinea-pig uterus method described above; it is absent if the pituitary has been previously extirpated. This work supports the histological evidence that pituitrin may pass *via* the stalk of the pituitary into the cerebro-spinal fluid, and presumably thence into the circulation.

According to Dixon, when certain substances are injected into animals the amount of pituitrin in the cerebro-spinal fluid is increased. These substances are (*a*) Pituitrin; (*b*) Duodenal extract, after a long latent period;

[1] Abel, however, claims that he has prepared a very potent "pituitrin" tartrate which gives *all* the physiological actions of posterior lobe extracts and which is 1000 times more powerful than histamine in its action on the guinea-pig uterus.

(*c*) Ovarian extract. Extracts of ovaries removed towards the end of pregnancy are most potent ; this activation of the pituitary is inhibited by corpus luteum extracts and by the presence of corpus luteum in the ovary extracted. The pituitrin content of the cerebro-spinal fluid is said to increase towards the end of pregnancy. Dixon suggests that as the corpus luteum of pregnancy degenerates, the rest of the ovary is free to stimulate the pituitary, and that the excess pituitrin in the blood causes the onset of labour.

Functions of Pars Intermedia.—We must distinguish between the pharmaco-dynamic effects of the extracts of a gland and the normal function of that gland in the body. A simple example will make this clear : Pituitrin contracts the uterus in labour, but that of course is not its function in the male body. Light is thrown on the normal function of the pituitary by extirpation experiments in animals and by the results of disease in man.

1. Regulation of Flow of Urine. –Experimentally, injury to the posterior lobe is often followed by the onset of an intense polyuria. A similar condition is observed clinically—*diabetes insipidus*—in which the urinary output is 10 litres or more daily. No abnormal constituents are present in the urine. (The condition should not be confused with diabetes mellitus, in which the polyuria is associated with glycosuria.) Subcutaneous injections of pituitrin check the polyuria and so relieve the condition. These observations, combined with the experiments recorded above, afford strong evidence that the posterior lobe normally checks the flow of urine and helps in the regulation of the water balance in the body (see p. 472, Water Intoxication).

2. Regulation of Metabolism.—There are a certain number of observations which suggest that the pituitary is related to metabolism. In acromegaly the metabolic rate is often raised, while in hypopituitarism it is usually lowered (p. 151). In acromegaly glycosuria and low sugar tolerance are common and death may occur in diabetic coma ; stimulation of the pituitary gives rise to glycosuria and so does injection of pituitrin ; in hypopituitarism excessive deposition of fat is usually observed. The following experiment (Cushing) suggests that the pars intermedia is concerned with these functions : the stalk of the pituitary is clipped (without interfering with the blood supply to the gland) ; the posterior lobe becomes very cellular and infiltrated with hyaline masses, appearances which may be interpreted as the result of obstruction to the escape of the secretion along the stalk. The operation is followed by the onset of *adiposity* [1] (and also of *polyuria*).

3. Control of Capillary Tone.—If the gland be extirpated in the frog, the capillaries lose their normal tone, become relaxed, and no longer undergo rhythmic changes in calibre. Tone can be restored to the capillaries by perfusing them with a weak solution of pituitrin. Whether the pituitary gland controls capillary tone in man is not certain, but pituitrin definitely constricts the capillaries in man and relieves certain states of shock which are characterized by loss of capillary tone (*e.g.* surgical shock and histamine shock). Krogh has demonstrated the presence of pituitrin in the circulating blood in mammals. (Cf. p. 292.)

4. Relation to Parturition.—*V. supra.*

[1] It has been suggested, too, that *adiposis dolorosa* (Dercum's disease) is a pituitary disorder. In this condition painful fatty deposits occur in middle-aged subjects, usually women. The overlying skin may be cold, cyanosed, and tender. There is considerable mental depression as well.

In the amphibians, pituitrin expands the pigment cells under the skin or *melanophores*. If the pituitary is extirpated, the melanophores contract, and thus considerable areas of skin are left free from pigment. The frog thus appears much paler than normal.

Functions of the Pars Anterior.—The pars anterior is the more important part of the pituitary body, and its presence is essential to life. Death results from complete extirpation of this part of the gland. The evidence available from clinical and experimental sources shows clearly that the anterior lobe stimulates *skeletal growth, sexual* and *mental development.*

Pathologically, increased pituitary secretion may occur (*hyper*pituitarism) or diminished activity (*hypo*pituitarism). A state of hypersecretion may later degenerate into a state of under-activity. Again, the two parts of the gland may be affected simultaneously but in different directions. To such complex derangements of function the term *dys*pituitarism is applied.

Hyperpituitarism.—Two conditions in which hyperpituitarism occurs are known—*gigantism* and *acromegaly*, in both of which tumours ("eosinophil" adenoma) of the anterior lobe of the pituitary are present (p. 145).

1. Gigantism is due to hyperpituitarism which develops before the union of the epiphyses of the long bones. In consequence, the bones continue to grow uniformly and become excessively long. Most giants who are seven or eight feet in height are examples of this disorder.

2. Acromegaly develops after the epiphyses have united. Hyperpituitarism is first present, and it then gradually passes into under-activity.

The principal features of acromegaly that concern us are :

(i) *Skeletal changes.*—There is overgrowth of certain parts of the skeleton, namely, the lower jaw, the upper jaw, and the malar bones (*i.e.* the lower half of the face); there is, consequently, separation of the teeth. The hands and feet are enlarged. There is bowing of the spine (kyphosis); the antero-posterior diameter of the chest is increased. The bent back, the big hands reaching down to the knees, the protruding lower jaw remind one of the very descriptive phrase—"a reversion to the gorilla type."

(ii) *Increased sexual excitement.* The above symptoms may be regarded as due to over-activity of the pars anterior.

(iii) *Glycosuria* of extreme variability may be present, which is apparently due to inability of the tissues to utilize sugar (some of these cases may die in diabetic coma); it is relieved by insulin. The glycosuria may perhaps be attributed to over-secretion of pituitrin (which antagonizes the action of insulin).

(iv) There is marked *connective tissue hyperplasia* the subcutaneous tissues of hands, feet, nose, scalp, and lips are markedly thickened; the skin is stiff and inelastic. Deep corrugations are present in the palms of the hands and on the scalp. *Sweating* is very profuse. The reverse changes are noted in hypopituitarism (p. 151) but no explanation of these symptoms is yet forthcoming.

When the disease progresses as it usually does to *hypo-activity* of the gland, certain differences are noted. The skeletal changes are, of course, fixed and cannot be affected. Sexual activity diminishes—the males become impotent and, in the female, the menstrual flow ceases. There is excessive deposition of fat in the subcutaneous tissues. Gradually increasing weakness develops, and finally death results.

The tumour may press on adjacent structures, *e.g.* on the decussating

fibres in the optic chiasma, causing loss of the temporal field of vision in each eye (p. 48), or on one optic nerve, causing unilateral blindness.

Hypopituitarism.—The principle features of this condition are: (i) *Depression of sexual function*: there is loss of sexual desire, impotence, or amenorrhœa. Thus in a boy of eighteen suffering from this disorder the voice was high pitched, the genitals were outwardly normal but no emissions occurred, and there was fullness of the breasts, hips, and lower abdomen. (ii) *Changes in skin and hair*: in the male the beard and axillary hair are scanty, the pubic hair is of feminine distribution, the trunk and limbs are hairless; in children the skin is smooth and delicate, in the adult dry, wrinkled, and atrophic; the secretion of sweat is diminished. (iii) *Adiposity* is fairly common, and there is a tendency for sudden fluctuations in weight to occur. In children the fat has a feminine distribution, but in adults the subcutaneous fat is grossly excessive in most regions. (iv) Stunted *skeletal* development. (v) *Mental backwardness.* (vi) *Lowered basal metabolic rate* (20 per cent. below normal on the average); this is associated with lethargy, slow pulse, and a moderate degree of somnolence. The blood sugar returns more slowly to its normal level after a carbohydrate meal, possibly because of the lowering of the oxidative processes in the tissues.

All or only certain of these features may be present in any individual case of this disorder.

The common clinical types are:

(*a*) *Fröhlich's* syndrome or "dystrophia adiposo-genitalis," in which all the functions of the pituitary are disturbed. It occurs in children, who become stunted and stupid or quite idiotic. The genitals are hypoplastic, and there are diffuse deposits of fat.

(*b*) The *Lorain* type: Mentally, these patients are normal, and their carbohydrate metabolism is unaffected; but the skeleton does not grow, and the secondary sexual characters do not appear. Physically they are like attractive and graceful children.

(*c*) The *Brissaud* type: The best known example in literature is the "Fat Boy" of Dickens. The subject is fat, with a round, chubby face; and is inclined to be slothful and sleepy. There is defective growth of hair on the chin and on the upper lip.

Active Principle of Pars Anterior.—Evans and Long administered extracts of fresh anterior lobe by intraperitoneal injection. They obtained almost giant-like rats; for instance, at the end of 333 days' treatment one of the injected rats weighed 596 grms. as compared with 248 grms. for the control of the same litter. The skeleton is larger and heavier. Œstrus, studied by the vaginal smear method (p. 171), is found not to occur or only at long intervals. The ovaries, however, are not underdeveloped, but are twice as heavy as those of the control animals, and exhibit many substantial corpora lutea. It appears that the follicles develop up to a certain stage, but *ovulation does not occur*; the follicles do not rupture and are prematurely transformed into corpora lutea, in the centre of which the ovum is still visible. The anterior lobe thus contains a growth-promoting substance, and one which, when given in excessive amounts to normal animals, stimulates lutein cell formation. Restoration of growth can be produced in hypophysectomized dogs and rats, and precocious œstrus has been induced in immature rats. Acceleration of growth

has also been observed in dogs receiving these extracts; the effects make their appearance very slowly. Thus one dog after daily injections for a period of eight months weighed 24 kg., against 17·5 kg. for the untreated litter-mate; acromegaloid changes also appeared in the injected animal. The extracts are inactive if given by the mouth. This suggests that oral administration clinically of commercial anterior lobe extracts cannot be of much avail.

Summary.—The pars anterior is essential to life. It controls skeletal, sexual, and mental development. An active principle has been isolated, but its chemical nature is not yet known.

Relation of Hypothalamus to Pituitary.[1]—It may be appropriate to discuss at this point the vexed question of the relation of the hypothalamus, particularly the region of the tuber cinereum, to the pituitary body. Puncture of the tuber cinereum gives rise to: (i) sudden increase in respiratory rate; (ii) often extreme rise of temperature—occasionally to 109° F.; (iii) glycosuria develops in a number of cases; (iv) polyuria sets in very regularly, usually 1 to 3 days after the operation. There is often a lack of balance between water intake and output; thus polyuria may be present with little drinking, or they may drink far in excess of their needs. In *chronic* cases, the adiposo-genital syndrome may develop; and clinically cases have been recorded of patients with tumours of the base of the brain who developed this syndrome in spite of an apparently intact pituitary. Cushing suggests that the tuber cinereum may be the *nervous centre controlling pituitary activity*; consequently damage to the centre, block to the nervous impulses from the centre to the gland, removal of the posterior lobe, or interference with the escape of the products formed by the gland might all yield similar results: and this seems to be the most satisfactory attitude to adopt. It is interesting to note that the polyuria which follows injury to the tuber is made worse by denervation of the kidney (owing to the dilatation of the renal vessels), an observation which suggests that the polyuria is due to lack of a substance circulating in the blood. Some workers believe that the hypothalamus also controls the activity of the sympathetic system.

THE THYROID [THYREOID] GLAND

Structure.—The thyroid consists of a framework of connective tissue enclosing numerous spherical or oval vesicles which are lined by granular cubical cells. The cavity of the vesicles is occupied by a homogeneous viscid material containing iodine—the colloid of the gland—which is secreted by the lining epithelium. In the new-born the gland consists of solid masses of epithelial cells, and no colloid is visible. The secretion is removed by the lymphatics, or it may pass directly into the blood stream.

The nerve supply of the gland is derived from the middle cervical ganglion of the sympathetic. Blood obtained from the gland after stimulation of the cervical sympathetic contains the active principle as can be shown by biological tests (cf. p. 155).

The thyroid gland forms an active principle—*thyroxine*—which facilitates and catalyses the oxidative activities of the body, and thus regulates the general level of metabolism.

[1] Cloake, *Proc. Roy. Soc. Med.*, 1927, p. 1643 (Bibliog.).

Extirpation Experiments.—The early extirpation experiments did not throw much light on the functions of the gland. The close anatomical relation between the thyroid and parathyroid glands was not recognized; and of course if the latter glands were removed as well, tetany set in early and proved rapidly fatal. Some animals, *e.g.* rat, rabbit, survived thyroidectomy, while others, *e.g.* dog, cat, succumbed as a general rule. It appeared that the actively preying carnivora were more dependent on their thyroid glands than the placid herbivora. It may be that in herbivora, as two of the parathyroids lie at a distance from the thyroid, tetany did not occur, and so the animals survived, while in the carnivora the parathyroids were unwittingly removed with fatal results.

Recent more careful investigation has shown that simple thyroidectomy in *adult* sheep produces few ill effects. Some thickening and dryness of the skin and a tendency to loss of hair and adiposity are noticed. Typical myxœdema (*v. inf.*), as found in man, is not obtained.

In *young* animals (lambs, rabbits) striking changes develop, closely resembling those seen in the human cretin (*v. inf.*).

(i) The skin becomes dry and thickened and the hair can be easily pulled out. (ii) Retardation of skeletal growth is marked. The long bones grow more slowly, and eventually attain much less than their normal adult length. The muscles are too flabby to support the body weight. The teeth are ill-developed. (iii) The generative organs remain small, and ova and spermatozoa may not mature. (iv) The nervous system is affected; dullness and apathy are prominent. Many of the nerve cells in the cerebral cortex exhibit a shrunken appearance.

Myxœdema.—In *man*, total extirpation of the thyroid gland in adult subjects produces a condition called "cachexia strumipriva" or *operative myxœdema*. The symptoms set in within a few weeks or months after the operation. An identical clinical condition of *myxœdema* occurs spontaneously in adults—especially in women—from atrophy of the thyroid gland. Minor forms of this disease are common. The gland is usually small, the vesicles are few, and contain little colloid. Fibrous tissue overgrowth may be present.

The chief symptoms can be readily understood if it is remembered that owing to lack of thyroxine all the activities of the body are depressed.

1. There is a diminution of mental activity, loss of memory, slowness of thought, speech, and movement.

2. The skin becomes dry and coarse. The cheeks are parchment-like in appearance and there is a slight malar flush. The hair tends to fall out on the head and over the outer thirds of the eyebrows. There is deposition of a peculiar firm myxomatous tissue (not fat, it is said) under the skin, giving a puffy appearance to the body. The patient feels the cold excessively.

3. The sexual functions are disturbed; amenorrhœa commonly develops in women.

4. The basal metabolism—*i.e.* the energy output of the individual at complete rest twelve to eighteen hours after a meal (p. 317)—is diminished by about 25 per cent., *i.e.* the rate of oxidation in the tissues is diminished. The pulmonary ventilation, the oxygen consumption, the CO_2 output, the

nitrogenous excretion in the urine are all diminished, because the general metabolic activities are depressed. As the tissues need less oxygen, the output of the heart is diminished to about 2·5 litres per minute (normal, 5 to 8 litres). This is due to slowing of the heart to 50 per minute and diminution of the output beat to 50 c.cm. (normal, 70 to 120 c.cm.). The body temperature is subnormal.

Cretinism.—In this condition there is congenital absence or maldevelopment of the thyroid glands from causes which are not definitely known. Symptoms do not appear till the age of six months possibly owing to the presence of sufficient thyroid substance in the mother's milk. The symptoms are as follows : (1) The various milestones in the course of the child's development—holding the head up, sitting up, walking, speech—are reached much later than normal. Mental development may be very backward, and the child be a complete idiot. (2) Bony growth is retarded. The skeleton is small and stunted. (3) The secondary sex characters do not develop. (4) The skin is thickened ; the tongue is enlarged and protrudes from the mouth ; deposits of fat appear, especially above the clavicles. (5) Constipation is commonly present. Owing to lack of thyroxine proper development of the body does not occur in the child, in the same way as all bodily activities are depressed in the adult. Both cretinism and myxœdema are greatly helped by the administration of thyroid extracts or of thyroxine.

Simple Goitre is a condition in which there is enlargement of the thyroid, accompanied as a rule by signs of *hypo*-thyroidism. There is diffuse overgrowth of the glandular tissue of the thyroid : the follicles are increased in number and in size. According to Marine the condition is due to *relative or absolute deficiency of iodine* in the food ; the glandular enlargement is regarded as a kind of compensatory hypertrophy (the gland is working harder in an attempt to make thyroxine under unfavourable circumstances).

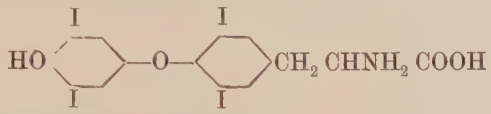
(1) *Absolute* iodine deficiency in food : goitre has been produced experimentally by total iodine deprivation ; it is endemic in certain areas where the soil, water, or food are deficient in iodine.

(2) *Relative* deficiency : in certain conditions, for reasons that are not clearly understood, the bodily need for iodine is increased, and unless this additional iodine is supplied goitre develops : (i) *puberty and pregnancy* ; (ii) *infections*, either general, such as tubercle, or local, such as tonsillitis ; (iii) certain *diets* (brook trout develop goitre on a diet of pigs' liver, pigeons on lard or other iodine-free digestible fat). Goitre in certain districts appears to result from a water-borne infection, and it is suggested that organisms thus introduced into the bowel " divert " iodine supplies which are otherwise adequate. The administration of 1 mgrm. iodine daily (in any form), prevents simple goitre (the maximum iodine content of the normal human thyroid is 25 mgrms.). The sudden administration of large amounts of iodine often causes the thyroid to swell and become firm and painful (" iodine thyroiditis "). This is due to rapid accumulation of colloid in the alveoli.

Thyroxine.[1]—Harington has determined the constitution of the active principle of the thyroid -thyroxine- -and has succeeded in synthesizing it.

[1] Kendall first applied the name thyroxine to a crystalline iodine-containing compound which he extracted from the gland ; it was a very active body, which he thought was closely related to the amino-acid tryptophane, and contained three iodine atoms. The later work of Harington revealed the true composition of the substance.

The empirical formula is $C_{15}\ H_{11}\ O_4\ Nl_4$; chemically it is a phenyl ether of the amino-acid tyrosine. The structural formula is :



Para hydroxy phenyl ether of tyrosine with 4 iodine atoms.

Thyroxine has a very remarkable effect on the metabolic activities of the body. Sixteen mgrms. of thyroxine were administered in one dose to a case of myxœdema in which the basal metabolism was 30 per cent. below normal. The energy output rose to normal and then slowly sank to its original level in about six weeks. During this period the extra energy given off in the body owing to the stimulus of thyroxine amounted to no less than 16,125 calories, or the amount which would be derived from burning 4·25 kgrms. glucose. Each milligramme of thyroxine thus increased the metabolism to an amount equivalent to the oxidation of about 250 grms. of glucose and was responsible for the liberation of 1000 calories. This gives some idea of how powerful a stimulus to the metabolism thyroxine is. The effect of thyroxine begins in a few hours after administration and reaches its maximum in several days. The normal rate of destruction of thyroxine in the body is 0·2–0·4 mgrm. daily ; this is therefore the dose required to restore a severe case of myxœdema to normal. The glycogen of the liver is mobilized, and so hyperglycæmia and glycosuria may result.

Thyroxine exerts identical effects if the adrenals have been previously extirpated, so that its action in no way depends on the intervention of these glands. A single enormous dose of thyroxine is harmless, while successive daily administrations may prove fatal.

A useful biological test for thyroid substance is its effect on tadpoles. Growth is suppressed and precocious differentiation of the body occurs. Metamorphosis begins a few days after treatment, and weeks before it takes place in the control animals. It is said, however, that similar results may be obtained with the iodides.

In *normal* mammals, administration of thyroxine in small doses produces (i) diminished rate of growth ; (ii) disappearance of the fat deposits ; (iii) hypertrophy of the organs chiefly concerned with the metabolic processes, *i.e.* liver, kidney, heart, adrenal (Cameron). Excessive thyroid feeding produces *toxic* effects : (i) loss of body weight ; (ii) gastro-enteritis and diarrhœa ; (iii) tachycardia. Exophthalmos has not been produced in this way.

Hyperthyroidism (Graves' Disease, Exophthalmic Goitre).—This disease is regarded as the result of excessive activity of the thyroid gland. In animals the phrenic nerve has been cut and joined up with the peripheral end of the cervical sympathetic, so that with each inspiration impulses passed down along the sympathetic and thus to the thyroid gland ; symptoms of hyperthyroidism developed, which disappeared on removal of the thyroid lobe on the same side (Cannon). It has been suggested that the secretion in exophthalmic goitre may possibly be *abnormal* in character, or a toxic element may be present as well. The original factor which causes the gland to function abnormally has not been identified, but emotional stress may play

a part. Some cases of simple adenoma of the thyroid may, at some stage, begin to secrete excessively and produce symptoms of hyperthyroidism.

1. The cardinal symptom is the *increased metabolic rate*, presumably owing to excessive secretion of thyroxine. The pulmonary ventilation, the oxygen consumption, the CO_2 output, the nitrogenous excretion in the urine are all increased as a consequence. The energy output at rest may in moderate cases be 50 per cent. above normal, and in severe cases 100 per cent. above normal. The circulation-rate is speeded up to enable larger quantities of oxygen to be supplied to the overactive tissues. In a case in which the metabolic rate was 65 per cent. above normal, the output of the heart was 11·7 litres per minute (normal, 5 to 8 litres). The output per beat was 116 c.cm., and the pulse-rate was increased (101 per minute) (Field and Bock). The cutaneous arterioles are relaxed and the skin is flushed and moist. Heat loss is thus increased and a rise of body temperature is prevented. The blood pressure varies—it is high in one stage of the disease and depressed at other times.

The work of the heart is increased and the diastolic rest period is diminished. It is not known with certainty whether thyroxine in excess may directly poison the heart muscle, but it certainly predisposes it to the baneful action of other toxins. As a result of cardiac overwork, hurry, and intoxication, signs of heart failure often supervene, and auricular fibrillation may develop.

The blood sugar may be raised and glycosuria is frequently present.

2. The *sympathetic* nervous system is *sensitized* and dilatation of the pupil, retraction of the upper lid, and protrusion of the eyes (exophthalmos) result.

3. A fine *tremor* of the voluntary muscles is present. It has been suggested that this is due to hyper-excitability of the motor nerves owing to coincident involvement of the parathyroid glands (Collip).

Operative removal of sufficient thyroid tissue usually cures the condition. The basal metabolic rate is the best guide to the amount of thyroid substance which must be taken away. It has been shown, however, that the administration of small amounts of *iodine e.g.* ℥xv of Lugol's iodine twice daily may lower the basal metabolic rate (B.M.R.) from +60 per cent. to +30 per cent. The clinical condition improves for about two weeks and the patient is better able to stand operative procedures; iodine medication also prevents the post-operative crises which often occurred with fatal results.[1]

Summary. The thyroid gland secretes thyroxine, which acts as a catalyst regulating the rate of the metabolism. If the hormone is formed in appropriate amounts, development takes place normally, and the various activities of the body proceed in their usual way. If it is formed in abnormal amounts, the metabolism is speeded up, as in Graves' disease, or depressed, if the hormone be deficient, as in cretinism or myxœdema.

[1] The mode of action of iodine is obscure. Plummer suggested that in Graves' disease a thyroxine poor in iodine is formed which is toxic; the administration of iodine results in normal thyroxine being made (though still in excessive amounts), and so beneficial results accrue. Marine thinks that the administration of iodine results (as it may do in simple goitre) in the accumulation of colloid in the alveoli of the gland, and the consequent rise of pressure in the vesicles temporarily interferes with the passage of the active secretion into the blood. Most observers find that the beneficial action of iodine does not persist for more than a few weeks, and then the metabolic rate begins to rise once more.

THE PARATHYROID [PARATHYREOID] GLANDS

The parathyroid glands are four in number normally. They consist of masses or columns of cells, with numerous wide vascular channels between them. The cells are of two types: 1. Principal or non-granular cells with faintly staining nuclei. 2. Few eosinophil cells with well-marked nuclei. The latter do not appear until puberty.

Considerable evidence has now accumulated that the parathyroid glands regulate the *calcium* level in the blood, or perhaps maintain the correct balance between the various ions in the blood.

Extirpation Experiments.—If the parathyroids are removed, a condition called "tetany" develops. It is characterized by *increased excitability of the motor nerves and of certain parts of the central nervous system.*

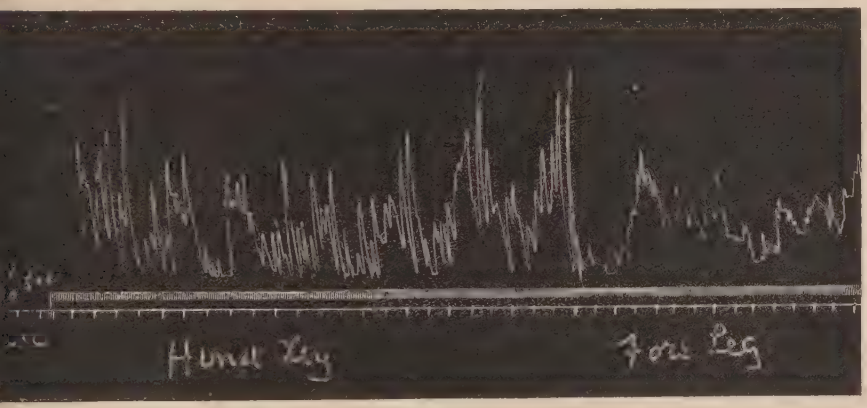


Fig. 51.—Parathyroid Tetany. (Paton.)[1]

Symptoms appear 1–3 days after the operation, and, in the dog, are as follows:

(1) *Peripheral Nerves.*—These are hyperexcitable to electrical and, to a less extent, to mechanical stimulation. This is well seen in the case of the phrenic nerve, which is apparently stimulated by the minute action current of the heart, for the breathing is synchronous with the rapid heart beat. The changes in the peripheral nerves are due to the altered state of the blood which bathes them: if the isolated limb of a dog is perfused with the blood of an animal in tetany, the characteristic hyperexcitability sets in.

(2) *Spinal Cord and Brain Stem.*—(i) The muscles show twitchings which at first are fine; later, coarse and irregular. The centre for the twitching movements is in the spinal cord, for they are still present in the distal part of the body of the spinal animal; they are abolished by section of the motor nerves (see Fig. 51).

[1] Figs. 51, 52, and 53 are reproduced from Sharpey-Schafer, *The Endocrine Organs*, 2nd edition (Longmans, Green & Co.), by permission of the author and the publishers.

(ii) Later, extensor stiffness develops in the legs; eventually violent *fits* occur, alternating as a rule with periods of depression. During the tonic stage of the fit the spasm of the respiratory muscles and larynx may produce fatal asphyxia, or death may result between the attacks from exhaustion. The centre for the convulsions is in the brain-stem. The symptoms of central origin (twitchings, fits) do not necessarily run parallel with the increased excitability of the motor nerves.

(3) *Involuntary Nervous System.*—This is also affected; there is spasm of the œsophagus and cardia; the response to the injection of adrenaline is increased.

(4) *Blood.*—The normal serum calcium is about 10 mgrms. per 100 c.cms. (the calcium content of the corpuscles has not yet been carefully studied); in tetany the serum calcium falls to 8 or 6 mgrms. This is the most constant chemical change in the blood. If intense hyperpnœa is present—as is so often the case—the washing out of CO_2 and the consequent alkalæmia tends to aggravate the condition (cf. p. 161 and legend to Fig. 65).

Relief of Symptoms. -(*a*) *Temporary.*—The intravenous injection of soluble calcium salts (or salts of the closely related metals barium, strontium, or magnesium) gives temporary relief; but the symptoms invariably return, with fatal results.

(*b*) *Permanent.*—The following measures produce permanent benefit and permit of indefinite survival: (i) 1·5 to 3 grms. calcium lactate per kgrm. daily by mouth; (ii) milk diet combined with large amounts of lactose, or with intravenous injections of $CaCl_2$; (iii) intravenous injection of 30 c.cm. Ringer's solution per kgrm. 4 to 8 times daily; (iv) the most effective measure consists of the appropriate administration of the parathyroid hormone. After 4 to 6 weeks of such treatment, the nervous system is found to have become adjusted to the altered state of the blood; if treatment is now discontinued, tetany no longer results, even with a serum calcium as low as 4 mgrms. per 100 c.cm.

If only one parathyroid be left, good health is maintained (except in young dogs, in whom such procedure is fatal). The condition of tetany is more marked in *young* than in *old* animals; in active *carnivora* than in *herbivora*; and on a *meat* diet.[1]

In the *pregnant* animal symptoms come on after complete parathyroidectomy in 8 hours, and death occurs in 24 hours. On a diet of lactose and milk symptoms are found to return during *œstrus* and *lactation* without change in the serum calcium (though during lactation there is loss of calcium in the milk).

Chronic Tetany.—Long-continued tetany is associated with striking changes in the metabolism of calcium. The teeth become soft and the dental enamel is lost. The bones are rarefied and readily broken. Fractures do not unite well. These observations suggest that the parathyroids are necessary for a proper deposition of calcium in osteoid tissue during periods of growth and repair. Opacities of the lens—*cataract*—are common.

The Parathyroid Hormone (Collip).—The hormone is prepared from fresh parathyroid glands, by extraction with 5 per cent. hydrochloric acid.

[1] A diet rich in meat can be tolerated if large amounts of calcium chloride are given as well.

The proteins are removed by precipitation at the iso-electric point.[1] The active principle is freely soluble in water, is soluble in alcohol up to 92 per cent. concentration, and is insoluble in ether. The extract can be administered subcutaneously or intravenously; it is probably not effective when given by the mouth. If adequate doses of the hormone are given to parathyroidectomized animals once or twice daily, tetany is prevented even when they are on a heavy meat diet. The serum calcium rises coincidently with the clinical improvement. Administration of the hormone may raise the calcium level from 7 to 15 mgrms., the effect appearing after a definite latent period. The serum calcium falls again quite slowly, so that one injection a day may keep the animal quite well. If a second injection is suitably spaced, summation of effects occurs and the serum calcium rises still higher. After 3 to 6 weeks, as stated above, treatment may be discontinued without ill effect.

The hormone not only cures parathyroid tetany in animals, but acts specifically in *infantile tetany*, presumably by raising the serum calcium. Cases of *nephritis* with marked œdema are said to show great improvement.

Hypercalcæmia (Collip).—If adequate doses of the hormone are given at intervals of two hours to *normal* animals, the serum calcium may rise to about 20 mgrms. per 100 c.cm. A striking series of symptoms results. There is loss of appetite, diarrhœa, dullness, drowsiness, and general muscular flaccidity. The blood becomes viscid and diminished in volume, and the circulation slowly fails. Coma develops finally. Intravascular clotting occurs immediately after death. As an abnormally low level of blood calcium produces hyper-excitability of the nerves, it might have been anticipated that too high a level of blood calcium would depress the nervous system.

The changes in the blood may be summarized thus: 1. Blood volume is diminished by 5 to 15 per cent. 2. Viscosity of blood is greatly increased. 3. Cl content falls gradually from 315 to 286 mgrms. per cent., *i.e.* about 10 per cent. 4. Urea nitrogen and non-protein nitrogen rise about 400 per cent., *i.e.* from 16 to 75 mgrms. and 43 to 162 mgrms. per cent. respectively. 5. Phosphate at first remains unchanged; just before the fatal issue it rises suddenly by over 100 per cent. The rise in blood nitrogen usually develops on the day following the onset of the hypercalcæmia; it is probably due to failure of renal activity; very similar changes in the blood nitrogen follow ligation of both ureters. A condition which closely resembles the syndrome just described may be produced by the *combined* injection of large amounts of $CaCl_2$ and acid sodium phosphate (NaH_2PO_4), but not by the administration of either substance alone.

Toxic Theory of Tetany.—Paton found that the injection of guanidine or methyl guanidine into animals increases the excitability of the motor nerves and may produce twitching or convulsions. In experimental tetany

[1] *Iso-electric point.*—If the colloid particles of a protein in solution are placed in an electric field they wander either to the anode or to the kathode, according to whether the solution is alkaline or acid. At a certain hydrogen ion concentration no movement takes place in either direction; this is called the iso-electric point of the particular protein. On the acid side of this point the protein behaves as a weak alkali and combines with acid radicles, *e.g.* Cl; on the alkaline side of this point it behaves as a weak acid and combines with basic radicles, *e.g.* Na (cf. p. 222). At the iso-electric point certain properties of the protein are at a minimum —*e.g.* solubility, viscosity, and osmotic pressure—and precipitation of the protein occurs.

the blood guanidine was said to be raised (but it appears that the chemical methods employed were unsatisfactory). On the basis of these observations, Paton concluded that the parathyroid glands regulate guanidine metabolism, and that if the parathyroids be removed, guanidine accumulates and produces tetany. This theory entirely fails to help in the understanding of the other forms of tetany which occur. Collip has found, too, that if convulsions are produced by the injection of guanidine into animals the condition is *not* relieved by administration of the parathyroid hormone as one would have expected.

The available evidence strongly suggests that the principle factor in the production of parathyroid tetany (and probably of other forms of tetany) is the lowering of the serum calcium. The fact, however, that a meat diet, gastro-intestinal derangement, or constipation, may convert latent into acute tetany does, however, suggest that a poisonous substance absorbed from the intestine may be a contributory factor. Similarly, the relief which is obtained from the injection of intravenous saline may be due to increased elimination of a poisonous body.

Tetany in Man.—As stated, by tetany we mean a condition characterized chiefly by heightened excitability of the motor nerves and of certain other parts of the nervous system. Defined in this way, tetany occurs in man in association with many superficially dissimilar clinical conditions. It may be "*latent*," and spasms are then only induced by external stimuli; or the tetany may be "*manifest*," and spontaneous attacks of tonic spasm occur, which may be limited to certain groups of muscles or involve the whole body. The term "*spasmophilia*" is employed by many clinicians as synonymous with tetany. Clinically the most striking manifestations of tetany are as follows:

1. Carpo-Pedal Spasm (Trousseau's Sign).—When slight pressure is applied to a limb, spasms occur either simultaneously or immediately afterwards. The hand passes into the "obstetric" position: the metacarpo-phalangeal joints are flexed, the fingers being extended, with the thumb in the palm. The wrist and elbow are flexed. In the case of the lower limb the toes are flexed, and the feet are drawn up.

2. Facial Irritability (Chvostek's Sign).—Tapping over the facial nerve after its exit from the stylo-mastoid foramen, results in contraction of the facial muscles.

3. Laryngismus Stridulus.—Without warning, the laryngeal muscles contract suddenly, and the glottis is closed. No air can enter the chest, and progressive cyanosis develops. After a variable period the spasm relaxes, and air enters with a "crowing" sound.

4. There is increased excitability of the motor nerves to the galvanic current. Normally a kathodal opening contraction (k.o.c.) can be obtained with a current of not less than 6 milliamperes. If contraction results from a current below 5 milliamperes, increased galvanic excitability is present. In tetany 0·6 milliamperes may be sufficient to produce a contraction. It has been shown by electrical methods that in infancy and childhood tetany occurs frequently in the latent form.

Causes of Tetany.—It must be remembered that tetany in man may result from many conditions, and may be associated with perfectly normal parathyroid glands. Much light has been thrown on the essential nature of

tetany by accurate investigation of the concentration of the various ions in the blood. It has thus been found that in tetany the serum calcium is lowered or there is incorrect balance between the different ions of the blood.

Calcium of Blood.—We must first consider briefly the state in which calcium exists in the blood. The subject is extremely obscure, and few dogmatic statements can be made. According to Howland, tricalcium phosphate $Ca_3(PO_4)_2$ is present in the serum, but it is relatively insoluble, giving rise to few free calcium ions. Under the influence of the carbonic acid of the plasma it is partly converted into the more soluble calcium bicarbonate $Ca(HCO_3)_2$ and calcium hydrogen phosphate $CaHPO_4$.

$$Ca_3(PO_4)_2 + 2H_2CO_3 \lesseqgtr 2CaHPO_4 + Ca(HCO_3)_2$$
$$\gtreqless 2Ca^{++} + 2HPO_4^{--} + Ca^{++} + 2HCO_3^{-}.$$

It is obvious that the amount of these soluble calcium salts present in the blood, and consequently the amount of calcium in the *active ionic form* (which is probably the physiologically important fraction), will depend on the carbonic acid tension. If, for any reason, the carbonic acid tension is reduced, the equations given will act from right to left, and some of the insoluble tricalcium phosphate is reprecipitated. Furthermore, in such an equilibrium as represented by these equations, a change in the concentration of *any* one ion will at once produce changes in the concentration of the other ions. The chemical conclusions from this statement may be summarized thus :

$$\frac{[Ca^{++}] \times [HCO_3^{-}] \times [HPO_4^{--}]}{[H^{+}]} = K \text{ (constant).}$$

A reduction in the CO_2 tension of the blood and so in the H ion concentration will lower the denominator in this equation, and therefore an equivalent diminution in the numerator must occur, *i.e.* the concentration of calcium, bicarbonate, or phosphate ions must correspondingly fall. Alkalæmia will therefore tend to lower the serum calcium, while acidæmia might tend to raise it. Further, if a fall in the serum calcium occurs primarily, one would expect to find a raised HCO_3^{-} or HPO_4^{--} content, or a diminished H ion concentration.

Tetany may result from (1) extirpation of the parathyroids, (2) alkalæmia, (3) rickets, (4) possibly in nephritis. In practically every variety of tetany there is a *lowering of the calcium level*, and also some *alteration of the other ions* of the blood, chiefly an increase of the phosphate and bicarbonate, or a diminished hydrogen ion concentration (see table, p. 162).

I. Parathyroid Tetany, (i) in animals following extirpation of the glands. The serum calcium is diminished and the phosphate is raised.

(ii) In man, following the removal of large amounts of thyroid substance, especially when in cases of malignant disease of the thyroid gland, the parathyroid glands happen to be removed by the extensive operation. The serum calcium is diminished and the phosphate raised.

II. Tetany from Alkalæmia.—(i) *Gastric Tetany.*—This develops in spite of normal parathyroid glands, and is associated with pyloric obstruction and profuse vomiting. The bicarbonate content of the blood is raised, and the blood reaction is more alkaline than normal. The alkalæmia may in some cases be due to loss of hydrochloric acid owing to vomiting (p. 226).

(ii) *Tetany from Hyperpnœa.*—Following excessive voluntary pulmonary ventilation, increased excitability of the motor nerves results, and even generalized spasms may occur. The carbon dioxide content of the alveolar air and the arterial blood is lowered; there is consequently increased alkalinity of the blood (alkalæmia), and the amount of active *ionized* calcium in the serum is perhaps diminished in amount (see Fig. 65, p. 226).

(iii) Tetany from excessive ingestion of *alkali*, *i.e.* sodium bicarbonate. This has occurred in the modern alkali treatment of gastric and duodenal ulcers. The bicarbonate content and the alkalinity of the blood are increased, and here too the amount of ionized calcium is possibly diminished.

III. Tetany and Rickets.—*Infantile Tetany.*—It is highly improbable that destructive changes occur in the parathyroid glands in this condition. Hæmorrhages are sometimes found in the glands, but not more frequently than in the case of children dead of other diseases. Infantile tetany, however, is invariably associated with rickets. In this latter disease, it is well known that the metabolism of both calcium and phosphorus is greatly disturbed; owing to deficiency of vitamin D in the food there is imperfect absorption of calcium, and so the serum calcium is often found to be lowered. We may regard infantile tetany, then, as an incidental accompaniment of rickets. The disturbed calcium and phosphorus balance usually affects the ossification of the bones only. If the excitability of the nerves is affected as well, tetany may result. Infantile tetany will therefore be ameliorated by such measures as will cure the rickets and so raise the serum calcium—*i.e.* an adequate diet, ultra-violet rays, etc. (p. 448). Tetany also occurs in *osteomalacia*, which may be regarded as a form of adult rickets (p. 450).

IV. In *nephritis* of a severe type there is lowering of the serum calcium and retention of phosphates. It is well known that fits occur quite commonly in this disease.

A table (modified from MacCallum) summarizes the findings in the blood in the different forms of tetany:

Types of Tetany.	Blood Analysis.			
	Calcium.	Bicarbonate.	Reaction of Blood.	Phosphate.
Parathyroid	Diminished.	Normal.	Normal.	Increased.
Post-operative	Diminished.	Normal.	..	..
Gastric	Normal.	Increased.	Alkalosis.	Increased.
Hyperpnœic	(?) Diminished.	Increased.	Alkalosis.	..
Alkaline	(?) Diminished.	Increased.	Alkalosis.	Increased.
Infantile	Diminished.	Normal.	Normal.	(?) Increased.

Summary.—The parathyroid glands play a very important part in regulating the calcium concentration in the blood, and in maintaining a proper balance between certain ions in the blood; they also influence the deposition of calcium in growing bone and osteoid tissue. Their mode of action is unknown. Tetany is characterized by hyperexcitability of the motor

nerves and of the central nervous system, and depends primarily on a lowering of the serum calcium; this may result from loss of the parathyroid secretion, from defective absorption of calcium from the bowel in rickets, from defective calcium absorption combined with increased calcium demands by the fœtus in osteomalacia (p. 450), or from increased alkalinity of the blood, which may reduce the amount of calcium present in the ionized and active form. In parathyroid tetany it is possible that some unknown toxin may contribute to the production of the symptoms.

THE TESTIS

The testis consists of seminiferous tubules which elaborate the spermatozoa, and interstitial cells to which has been attributed the internal secretion of the organ.

Structure.—1. The *seminiferous tubules* are surrounded by a thin

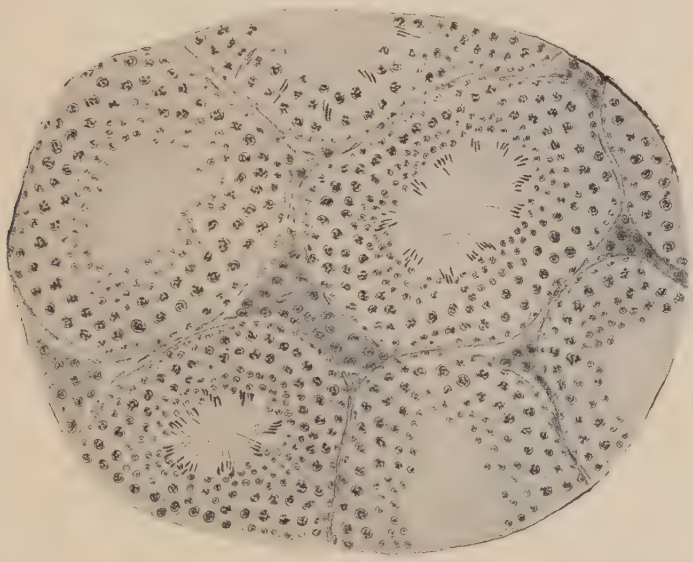


Fig. 52.—Normal Testis. Tubules show spermatogenesis. Some interstitial cells between the tubules.—Sharpey-Schafer.

connective-tissue membrane, and are lined by several layers of cells. Named from without inwards they are *spermatogonia*, *spermatocytes*, small cells or *spermatids* which become elongated and converted into *spermatozoa*. Between the spermatogonia are elongated *cells of Sertoli* which project into the lumen of the tubule, and to which the developing spermatozoa are attached (Fig. 52).

2. The *interstitial cells* develop from the mesoderm of the embryo. They are abundant in the fourth month of fœtal life, or period of the "first puberty" when the undifferentiated or "asexual embryonic form" is

moulded into one or other sex. In the new-born the interstitial cells are fewer and diminish until ordinary puberty (" second puberty ") is reached. There is an increase in their number again with the onset of spermatogenesis. They remain constant in number during sexual life, and diminish during later life. It is said they again increase in old age when the sexual power may be temporarily increased. The interstitial cells are definitely epithelial in appearance, with rich protoplasm and well-marked nuclei. They are usually arranged round the blood vessels. Material with characteristic staining reactions is said to pass into the intercellular spaces and thence into the capillaries.

Extirpation Experiments.—1. Before Puberty.—If the testes are removed, the rest of the reproductive apparatus does not develop. The vesiculæ seminales and the prostate are small and atrophic. The secondary sex characters do not appear. There is no growth of hair on the face, trunk, or axillæ. The pubic hair is of the female type, the outline being concave upwards. The growth of the larynx is arrested. The mentality is peculiar and marked depression is often present. There is a tendency to gigantism. The bones of the limbs are *longer* and stronger, the whole skeleton is bigger, and the epiphyses unite late. There may be abnormal deposition of fat; accumulations may be found on the buttocks, hips, pubes, and breasts.

2. After Puberty.—Except for the fact that no skeletal changes occur, the phenomena are very similar to those already described. The penis, however, remains of normal size, and so is usually amputated in the case of Eastern eunuchs. Sexual feeling is usually lost, though an imperfect kind of erection of the penis may sometimes occur.

Tying the Vas Deferens.—If the vas [ductus] deferens is ligated, no changes occur in either the somatic or the psychical sexual characteristics. The seminiferous tubules are found to undergo degenerative changes. The interstitial cells persist as definite masses of epithelial cells (Fig. 53). If this interpretation of the histological findings is accepted, it follows that the interstitial cells are responsible for an internal secretion which controls the secondary sexual characters. Steinach has attempted to make use of these results and to " rejuvenate " senile rats by tying one vas deferens. The underlying idea of this method of treatment is as follows: The seminiferous tubules of the affected testis would atrophy, and the interstitial cells having at their disposal an excess of nutritive material would proliferate. Their internal secretion would be manufactured on a bigger scale. Passing into the blood stream it would produce general psychic and somatic changes, and reaching the opposite testis it would stimulate its seminiferous tubules and restore the reproductive power. Steinach claims that he has obtained the expected results both in animals and in human subjects, but his work has not yet been generally confirmed.

Cryptorchidism.—If the testis fails to descend into the scrotum the seminiferous tubules remain infantile in structure and no development of spermatozoa takes place. The interstitial cells usually show hypertrophy. If the condition is bilateral the individual is sterile, but the secondary sexual characters develop normally. It has been suggested that the lack of development of the seminiferous tubules in the cryptorchid is due to the higher temperature to which the gland is exposed in the abdomen as compared with the scrotum; if the scrotum is kept artificially warmed, or if the testis

is deliberately transferred to the abdomen, spermatogenesis is said to cease.

Grafting Experiments.—Voronoff has grafted testes into castrated and senile animals, and found that they improved in condition and regained their lost vigour and their secondary sexual characters. For his human work he employs the testes of the higher apes. The testis is divided into two to eight portions, the tunica albuginea is scarified to cause exudation of fluid, and the graft is then sutured with catgut within the tunica vaginalis. In successful cases it is claimed that very striking results are obtained from this operation. Old people, with marked signs of senility, are claimed to be thus transformed into vigorous energetic individuals. Previously castrated persons may

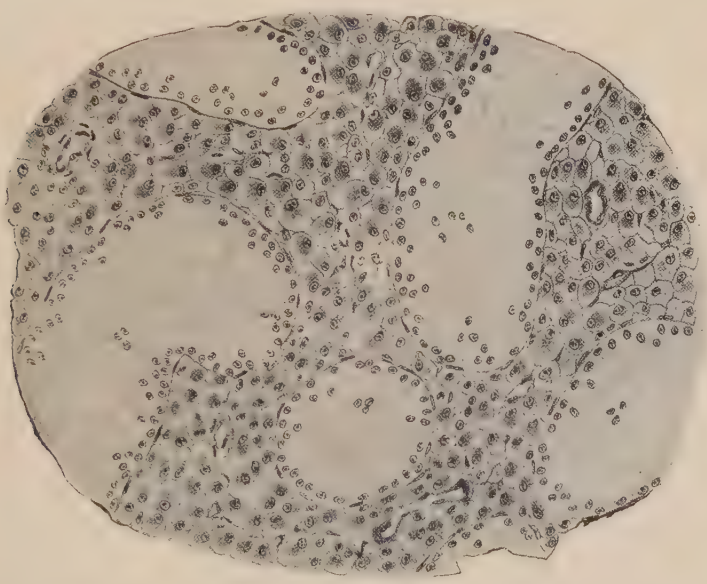


FIG. 53.—Testis. Effect of tying vas deferens. Seminiferous tubules atrophied, interstitial cells greatly hypertrophied. (ANCEL and BOUIN.)

regain their secondary sex character —*e.g.* growth of beard and moustache may occur. If the transplant is made under the skin or into the substance of muscles, it is rapidly absorbed. The fate of the scrotal grafts was carefully studied. After one year, in a successful animal experiment, the graft is found to be quite vascular. The seminiferous tubules have disappeared and been replaced by solid syncytial masses surrounded by connective tissue. Nothing resembling interstitial cells is found (Fig. 54). Voronoff claims that the syncytial masses of protoplasm with deeply staining nuclei represent transformed seminiferous tubules, which no longer elaborate spermatozoa, but still continue to furnish the internal secretion.

It is quite clear that there are two diametrically opposed views as to the source of the internal secretion of the testis, based on conflicting histological

observations. Some workers attribute the internal secretion to the interstitial cells and others to the epithelial lining of the seminiferous tubules.

While Voronoff's operation appears quite justifiable in young subjects in whom the testes have been damaged or destroyed by injury or disease, the treatment of senility by this method is more questionable. We have no proof whatever that senility is solely due to atrophic changes in the testis; it is almost certain that many other factors are concerned. Though the testicular graft may stimulate physical activity and sexual desire, it cannot restore the worn heart, arteries, and essential organs to their normal state.

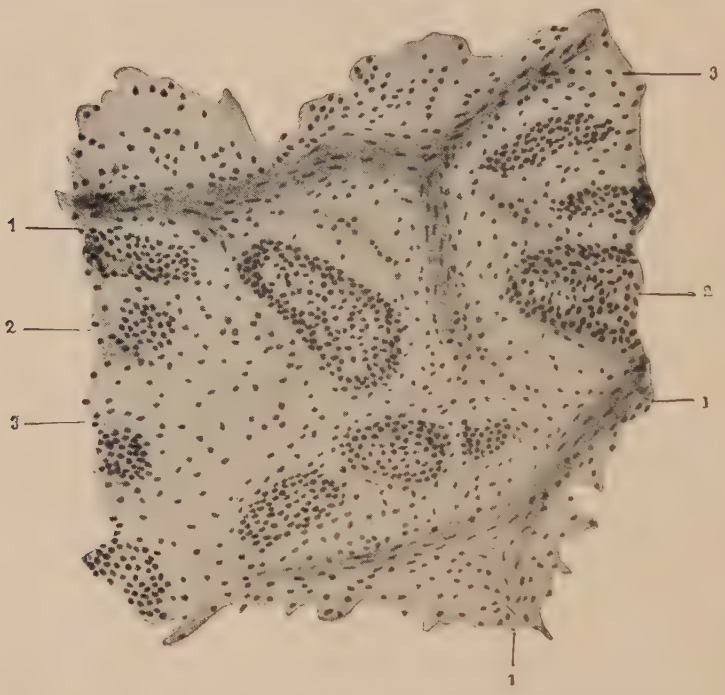


Fig. 54.—Section of Testis 14 months after Grafting.—After Voronoff.

1, 1, 1, Fibrous strands; 2, 2, Remains of seminiferous tubules; 3, 3, Loose connective tissue.

There is grave danger that excessive strain may be put on damaged structures, with disastrous results.

The following observations suggest that the interstitial cells may be mainly a storehouse of nutriment:

1. At three months of age, before the sexual characters have appeared, the testis of the cock contains many interstitial cells. At six months, when the sex characters are well developed, the interstitial cells are no longer present.

2. The mole has a short breeding season during the months of January and February. In the autumn the tubules are in a resting state, and the interstitial cells occupy about four-fifths of the substance of the testis. In

January the tubules increase in size and the interstitial cells become inconsiderable. In other words, the interstitial cells are least well marked during the period of greatest sexual activity.

Stieve has suggested that the interstitial cells are simply trophic cells taking up nutriment from the blood and passing it on to the tubules. They also store nutriment in readiness for the rutting season. This would explain the findings in the mole. In man, who is capable of reproducing all the year round, no sudden demands are made by the tubules, and so the warehouse of interstitial cells is small. It is premature, however, to attempt to come to any final decision in the matter.

Relation of Testes to Other Ductless Glands.—1. The thymus normally persists till puberty, when the reproductive organs develop. Castration has been found to prolong the period of persistence of the thymus. The sex glands therefore exert a depressant effect on the thymus (p. 177).

2. If small doses of radiation are applied to young animals they become very obese. The seminiferous tubules are found to atrophy and the interstitial cells to hypertrophy. Changes are then present in all parts of the pituitary body. It is suggested that the proliferated interstitial cells depress the activity of the pituitary and thus cause obesity.

3. There is evidence that both the pituitary and thyroid secretions stimulate the activity of the reproductive organs (pp. 150, 154).

4. In cases of tumours of the adrenal cortex, sexual precocity or reversion to the male type of secondary sex characters has been noted (p. 127).

THE OVARY

Structure. — The Graafian Follicle. — The ovary is covered by a layer of small cubical cells called the germinal epithelium. Down-growths of this epithelium take place, forming the egg tubes of Pflüger. They are cut off from the surface and undergo further development to form the *Graafian follicle* [vesicular ovarian follicle]. One of the cells enlarges and eventually becomes the ovum ; the others arrange themselves around it as the membrana granulosa. The membrana granulosa proliferates, forming many layers of cells. Fluid begins to appear in these cells, first as droplets, which rapidly coalesce to form a cavity containing the liquor folliculi, which separates the layers of the granulosa. Finally the follicle consists of a large cavity lined by two or three layers of flattened cells, and containing the ovum, attached by a mass of cells (discus proligerus [cumulus]) to one pole of the follicle. The stroma of the ovary, which consists of irregularly arranged spindle-shaped cells, differentiates into two layers surrounding the follicle : an inner tunica vasculosa, and an outer fibrous tunic.

More fluid exudes into the follicle, and the pressure within it rises. The ovarian substance which separates it from the surface necroses and gives way, and the follicle ruptures. The ovum and liquor folliculi escape into the peritoneum. This process is known as " ovulation." It occurs between the thirteenth to seventeenth day after the first day of the menstrual period in the human female. The corpus luteum matures on the nineteenth day and persists to the twenty-seventh day. It degenerates on the twenty-eighth day and during menstruation.

In infants, the rupture of the follicle does not occur. The ovum is removed by a process of phagocytosis, probably by the cells of the granulosa. A species of granulation tissue develops from the tunica vasculosa which absorbs the contents of the follicle, and is itself finally converted into a fibrous scar.

Corpus Luteum.—After ovulation the lining membrane of the follicle collapses into a folded layer. The sudden relief of tension causes the blood vessels of the vascular tunic to give way, and hæmorrhage occurs into the cavity of the follicle. The blood coagulates, and is replaced by ingrowing cells, which form the corpus luteum. These cells are derived either from the stroma of the ovary or from the remains of the membrana granulosa, probably the latter.

The fully developed corpus luteum consists of columns of large pointed epithelial cells, with well-marked nuclei, and yellow pigment (lutein). Between the cells are strands of fibrous tissue and small blood vessels. If pregnancy ensues, the corpus luteum grows for several months and attains a large size. If pregnancy does not occur, the luteum cells degenerate, and are removed and replaced by a fibrous tissue scar.

Interstitial Cells.—These are more conspicuous than the corresponding cells of the testis. When well developed, they consist of typical epithelial cells, without ducts, and with an abundant blood supply. The cells are polyhedral in shape, and contain numerous granules, chiefly of a lipoid nature, which may represent their secretory product. They are not found at all in about half the species which have been examined. They are said to become differentiated from the spindle-shaped stroma cells, or to develop from the lining membrane of follicles which have not ruptured.

Menstruation and the Œstrous Cycle.[1]—The body of the uterus consists of the following layers from without inwards: (1) serous coat; (2) thick muscular coat supplied by the sympathetic (see p. 122); (3) thick mucous membrane or *endometrium*, which undergoes characteristic changes during the menstrual cycle in the human female. Four stages may be recognized:

1. Resting Stage (about 12 days).—There is an intact *ciliated* columnar epithelium which dips down into the mucosa in the form of simple tubular glands between which is the stroma, consisting of loosely arranged connective tissue cells.

2. Constructive Stage (about 5 days).—The endometrium becomes considerably thickened. The glands enlarge and become distended with secretion, the stroma cells proliferate and become more closely packed, the capillaries become congested (*premenstrual congestion*), and exudation of clear or blood-stained fluid occurs.

3. Destructive Stage (4 to 5 days of *menstruation*).—Blood passes out freely from the capillaries, partly by diapedesis through intact vessels and partly through areas where the lining wall has broken down. The blood lies in the stroma, bursts into the lumina of the glands, and accumulates in considerable quantities beneath the superficial epithelium; it finally reaches the uterine cavity by stripping off varying amounts of the lining epithelium, and passes to the exterior, together with much mucus from the uterine glands, migrated leucocytes, and fragments of disintegrated mucosa.

[1] See Marshall, *Physiology of Reproduction*, London, 1922, 2nd ed. pp. 32–108, 156–158.

The menstrual discharge does not usually clot (owing to the alleged absence of thrombin), though it is said to be rich in calcium.

4. Stage of Repair (about 7 days).—The blood which is present in the stroma is absorbed and the denuded epithelium is replaced by proliferation of the remaining cells and those of the glands ; the vascular engorgement and œdema disappear.

In the lower animals sexual activity is usually limited to certain periods of the year[1] ; in the non-breeding season or period of rest (*anœstrous* period) the uterus is relatively anæmic and the animal shows no disposition to seek out its mate. The *sexual season* is divided into a variable number of *œstrous cycles* which consist of these stages : (1) *Pro-œstrum*—the uterus is congested and blood may escape to the exterior. (2) *Œstrus*—the special period of desire in the female, the only time when she will receive the male or fruitful coitus is possible. (3) If pregnancy does not ensue, the changes in the generative organs subside (*metœstrum*). In the absence of successful coitus the œstrous cycle is repeated in the rat every 4 to 5 days (polyœstrous animal) ; in other animals the œstrous cycle may occur once only during the sexual season (dog).

The menstrual period probably corresponds to the pro-œstrum of the lower mammalia, and may perhaps be regarded as a period of preparation for the embedding of an ovum in the uterine wall ; though conception can occur throughout the inter-menstrual period, it is said that the period of greatest sexual desire and greatest fertility is the week following the period ; this time would correspond with the stage of œstrus.

Extirpation of the Ovary.—1. Before Puberty.—Little is known of the effects of extirpation of the ovary before puberty in the human subject. Probably puberty does not set in, the menstrual flow does not appear, and the secondary sex characters do not develop. The normal appearance of puberty, therefore, depends in part on the activity of the ovary. At this time the secondary sexual characters of the female appear, and are demonstrated by increased growth of the genital organs, and the appearance of hair in the axillæ and on the pubes. The curves of the body become rounded, the breasts enlarge, and there are certain psychic manifestations. It is probable that other ductless glands, especially the thyroid (p. 154) and pituitary (p. 150), also play some part in this process.

2. After Puberty.—Following extirpation of the ovary, there is atrophy of the whole genital apparatus—the uterus, the vagina, and the external genital structures. Menstruation ceases permanently. The effect on the breasts is variable. They may increase in size, owing to local accumulation of fat, or they may shrink because the glandular tissue atrophies. Obesity develops from diffuse deposition of fat. Varying reports are given concerning the effect on sexual desire, but apparently it may not be much affected. There is considerable emotional disturbance, varying from a certain amount of irritability or depression to a condition closely allied to insanity.

The *menopause* or *climacteric* is the period of life when menstruation naturally ceases, and other phenomena identical with those just described make their appearance. The time at which this usually occurs is between the ages of forty-five and fifty, although it may occur earlier or later. The

[1] Primitive man, according to some authorities, is said to have had a restricted sexual season which may have been limited to the spring.

condition is associated with definite changes in the ovaries. They become smaller, the Graafian follicles disappear, and, microscopically, are seen to consist, chiefly, of fibrous tissue.

Grafting Experiments.—When the ovaries are grafted into an ovariotomized subject, they may function for a time, usually for about twelve months. During this period they remain normal in structure, and undergo cyclic ovulation. Degeneration then sets in, affecting first the corpora lutea, then the follicles become cystic, and finally, the interstitial cells disappear. When these latter cells degenerate, atrophy of the genital organs is said to set in.

Feminizing Experiments.—If ovaries be transplanted into young male rats three or four weeks old, the graft as a rule fails. The testis appears to exert an antagonistic influence on the implanted female gonad, and interferes with its nutrition. It is necessary first to castrate the male, and to allow several weeks to elapse so that the animal has time to become sexually indifferent. The ovaries are then transplanted on to the peritoneal surface of the abdominal wall, the surface being scratched to induce hyperæmia. If the graft succeeds, the following results are obtained :

1. The mammary glands, which are normally rudimentary in the male, are stimulated to increased growth, and may secrete milk and suckle the young.
2. Body conformation proceeds in the female direction.
3. The penis becomes smaller than in the castrated male animal, and is too short to be protruded.
4. The nervous system is " eroticized " in the female direction, and the animal is treated as a female by males.

The above experiments and observations indicate that the ovary is responsible for—

1. The normal onset of puberty.
2. The appearance of the secondary sexual characters.
3. The nutrition of the genital apparatus.
4. Menstruation.

It has been suggested that the interstitial cells of the ovary are responsible for these functions. The evidence for this statement, however, is very unsatisfactory (cf. p. 166).

The Ovarian Hormone.—Recent work has shown that it is possible by suitable methods to extract a chemical substance (" *œstrin* ") from whole ovaries which will produce precocious puberty in young animals and induce artificial œstrus in ovariotomized adult animals. Fresh ovarian substance is treated with alcohol to precipitate the proteins. The lipoids are removed from the alcoholic extract by means of acetone and digitonin. An oily residue is then obtained which is insoluble in water, but can be emulsified in weak sodium carbonate solution or be dissolved in olive oil ; it can be obtained from liquor folliculi, and from ovaries from which the liquor folliculi had previously been aspirated. The active principle appears to be equally distributed throughout the ovarian substance. It is a remarkable fact that the active principle can be readily obtained from placenta. The significance of this observation is not clear.

Method of Standardization.—As a result of the observations of Stockard and Papanicolaou the œstrous cycle in the small laboratory animals can be readily followed by examination of vaginal smears. With the onset of

pro-œstrus the uterus and vagina become very congested and distended with clear fluid, and the smear shows nucleated epithelial cells. When œstrus is at its height the vagina is almost perfectly dry. The vaginal epithelium has multiplied and become keratinized, the superficial lining cells are shed and appear in the smear as non-nucleated faintly staining or eosinophil flakes. The presence of these cells is a certain sign of œstrus. When œstrus passes off, numerous leucocytes appear. In the resting stage the vaginal smear shows degenerated leucocytes, broken down epithelial cells, and strands of fibrin.

To standardize the ovarian hormone (" œstrin "), adult rats are ovariotomized and the minimum dose found which will produce artificial œstrus. The ovarian extract must be injected subcutaneously and takes about thirty-six hours to produce its effects. When administered by the mouth the hormone is inert, unless given in enormous quantities.

In the rat, before puberty sets in, the vagina is represented by a solid column of cells. With the onset of puberty, this strand of cells undergoes degenerative changes, with the consequent production of a definite vaginal passage. Normal puberty occurs in a rat at the age of two or three months. By means of the active principle prepared in the way described, precocious puberty can be produced in quite young animals long before the normal time.

Properties.—The substance is a light viscid oil, soluble in chloroform and ether. It is insoluble in water, but dissolves in oils like olive oil. An active substance can be prepared which is quite free from cholesterol. It is thermostable and is fairly resistant to mild hydrolysis with dilute acids or alkalis. Tryptic digestion fails to destroy its activity. Recently it has been claimed that a water-soluble active substance has been isolated (Dodds).[1]

By daily injections of adequate doses of the hormone it is possible to maintain an almost continuous œstrus state for nearly fourteen days.[2]

The hormone appears to be antagonistic to insulin. It is known that diabetic women during the menstrual period require larger doses of insulin to keep the blood sugar down Animals during œstrus can withstand much larger doses of insulin without developing symptoms of hypoglycæmia than non-œstrus animals.[2]

Functions of the Ovary during Pregnancy.—It is believed that during pregnancy the ovary is responsible for—

(*a*) The embedding of the ovum and the development of the placenta.

(*b*) The growth and development of the breasts.

Most authorities hold that these changes are due to the activity of the *corpus luteum*, which is probably also responsible for the cessation of ovulation during pregnancy.

1. Cessation of Ovulation.—Ovulation does not continue during pregnancy. It is said that the injection of extracts of corpus luteum in suitable doses will prevent ovulation in fowls and arrest the onset of the œstrous cycle in rats; (further, the onset of menstruation coincides with the degeneration of the corpus luteum).

2. Embedding of the Ovum.—In rabbits, spontaneous ovulation does not occur. During coitus, however, the follicles are ruptured, the ovum is shed, and a corpus luteum develops subsequently. L. Loeb produced

[1] Dodds, *Lancet*, 1928, vol. i. p. 1107.

[2] Dickens, Dodds, and Wright, *Biochem. Journ.*, 1925, vol. xix. p. 853.

corpora lutea by allowing copulation to occur with bucks which had been sterilized by tying the vas deferens; or else he allowed normal copulation after tying the Fallopian tubes, thus ensuring that fertilization did not take place. If foreign bodies were then introduced into the uterus, or mechanical stimuli were applied to the mucous membrane, a placenta appeared at the point of stimulation which he termed an "artificial deciduoma." These results could only be obtained while the corpus luteum persisted.

Loeb concludes that the corpus luteum pours out an internal secretion which *sensitizes* the uterine mucous membrane in some way, so that it responds to mechanical stimulation by increase in thickness. Under normal circumstances the stimulus is set up by the presence of the ovum. In his experiments he found that even in the absence of special stimuli, the uterus showed slight deciduomatous development, presumably as a result of the ill-defined stimuli which occur in normal life.

3. Growth of the Mammary Gland.—If corpora lutea be formed artificially by the method just described, it is found that the mammary glands enlarge for fourteen days, and then atrophy—the period of development corresponding to the period of growth of the corpus luteum. It has also been shown that the enlargement of the breasts during each menstrual cycle has its parallel in the growth of the corpus luteum. Extirpation of the corpus luteum during pregnancy leads to regressive changes in the breasts. Injection of ovarian extracts is said to cause changes in the mammæ (see p. 173).

An intact nerve supply is not essential for the growth of the gland during pregnancy. The breast has been completely transplanted, thus severing all its nervous connections, and yet was found to grow during pregnancy, and to function, although somewhat inefficiently, after parturition.

The Active Principle of the Corpus Luteum.—The yellow pigment of the corpus luteum (lutein) is said to be isomeric with xanthophyll, which can be obtained from the chlorophyll of plants: the active principle has not yet been isolated. It is believed to be of a lipoid nature, but it certainly is not cholesterol.

Summary.—An active principle can be obtained from the ovary which can produce precocious puberty in young animals and artificial œstrus in ovariotomized animals. The substance in the corpus luteum which inhibits menstruation and which is responsible for the embedding of the fertilized ovum in the uterus and the development of the breasts during pregnancy has not yet been isolated.

THE SECRETION OF MILK[1]

Structure of Mammary Gland. The mammary gland consists of a series of *ducts*, which branch to give rise to *terminal tubules*, which in turn lead to the *alveoli*. Surrounding the ducts and to a lesser extent the alveoli are scattered cells which are thought to be modified muscle fibres.

The breast arises as an invagination from the surface epithelium which

[1] See Marshall, *op. cit.* pp. 586 622; Sharpey-Schafer, *Text Book of Physiology*, 1898, vol. i. p. 662; Meigs, *Physiol. Rev.*, 1922, vol. ii.; Loeb in Cowdry, *Special Cytology*, vol. ii. p. 1175 (New York, 1928); Holt and Howland, *Diseases of Infancy and Childhood*, 9th ed. (New York, 1926).

dips down into the underlying connective tissue, first as solid columns of cells which gradually become hollowed out to become ducts. At *birth* the breast is rudimentary ;[1] before puberty development is slow and consists chiefly of elongation and slight lateral branching of the ducts. At *puberty*, in the female, in consequence of ovarian activity (p. 169) marked branching of the ducts occurs and alveoli develop in certain species, though perhaps not in the human being. With each sexual cycle the gland undergoes further proliferative changes with subsequent regression, but on the whole progressive enlargement takes place, which is due in part to increased deposition of fat. Between the *menstrual periods* there is hyperæmia of the breasts, increase in the interalveolar stroma, and possibly new formation of alveoli ; these changes are transient because the corpus luteum which gives rise to them soon degenerates (p. 167). The intense proliferative changes which occur during *pregnancy* are due to the persistent corpus luteum (p. 172) ; growth of the gland occurs mainly during the early part of pregnancy. The cells then undergo differentiation and may begin to secrete even before the birth of the young.

Secretion of Milk.—This is probably due to several factors : (i) the alveoli of the breast are fully mature ; (ii) with the degeneration of the corpus luteum a possible inhibitory influence that it exerts on secretion is removed ; (iii) mainly, however, the process is set up by the suckling of the infant. The secretion of small amounts of milk takes place during the latter part of pregnancy, for a few drops of milk can usually be expressed from the breasts at this time. The milk accumulates in the galactophorous ducts, and when a certain tension has been reached, further secretion by the gland alveoli is checked. If the ducts are emptied by the infant, or by mechanical means, fresh secretion of milk occurs. The quantity of milk secreted is thus regulated by the needs and strength of the infant. Besides acting directly on the breast, as suggested, suckling may also set up *reflex* secretion.

Suckling is said reflexly to cause tonic contraction in the uterus, and thus to aid involution, after parturition. Hyperinvolution may follow excessive suckling.

Composition and Properties of Milk.—Human milk is a sweetish, bluish white fluid, amphoteric to litmus, and slightly acid to phenolphthalein. Its specific gravity averages 1031 at 60° F. If acetic acid be added, slight precipitation occurs in the form of fine flocculi, never in the form of large firm masses, as is the case with cow's milk. Microscopically, numerous fat globules and some granular matter can be seen ; and rarely, a few epithelial cells which have been shed from the ducts or the nipple.

Colostrum.—This is the name given to the fluid secreted during the first three days after parturition. It is deep yellow in colour ; the specific gravity is 1030 to 1035 ; the reaction is strongly alkaline, and it is coagulated into solid masses by heat, and may even coagulate spontaneously. It contains large granular bodies, about five times the size of fat globules, called *colostrum corpuscles*. These represent either discharged alveolar cells of the gland, or else leucocytes loaded with fat. These corpuscles are abundant in the first few days, and disappear at the end of the second week.

[1] Secretion of a fluid which resembles colostrum (*v. supra*) may occur in the new-born ; it is attributed to slight proliferation in the gland of the fœtus just preceding birth owing to the stimulating action of the corpus luteum of the mother.

Colostrum is rich in protein and salts. The milk formed during the first few weeks is called the "intermediate" or "transition" milk. "Mature" milk appears at the end of the first month.

The accompanying table (from Holt) indicates the composition of human milk at different stages, and compares it with cow's milk:

	Protein.	Sugar.	Fat.	Ash.
	Per cent.	Per cent.	Per cent.	Per cent.
Colostrum	8·5	3·5	2·5	0·37
"Transition" milk	2·25	7·5	3·0	0·3
"Mature" milk (average)	1·25	7·5	3·5	0·2
,, ,, (normal range)	1·0–2·0	6·5–8	3·0–5·0	0·18–0·25
Cow's milk (average)	3·5	4·75	3·5	0·75

The differences between human and cow's milk are very striking. Human milk contains considerably less protein and less salts and more sugar.

1. The *protein* content of milk is highest in colostrum (8·5 per cent.), and falls during the first few weeks (2·25 per cent.) to reach a fairly steady level of about 1·25 per cent. It diminishes rapidly towards the end of lactation. Two proteins are found:

i. *Caseinogen* is precipitated by weak acids and converted by rennin into insoluble calcium caseinate (p. 443), which is easily dissolved by gastric juice. It contains all the essential amino-acids except cystine.

ii. *Lactalbumin*: resembles serum albumin. It is rich in cystine.

In human milk there are about two parts of lactalbumin to one part of caseinogen. In cow's milk the proportions are very different: the caseinogen is six times in excess of the lactalbumin. Cow's milk therefore contains about twelve times as much caseinogen as human milk; furthermore, this caseinogen forms large solid masses in the stomach which are relatively insoluble. Its chemical composition, too, is different from that of human caseinogen.

2. *Fat* exists in milk in the form of minute globules which are emulsified by the dissolved albumin. The fats chiefly present are triolein, tristearin, and tripalmitin. Free fatty acids are only found in minute amounts. Cow's milk contains about eight times as high a fatty acid content, which makes it less digestible.

3. The *ash* contains Ca, Cl, and oxides of P, K, Na, and possibly traces of iron. The very *low iron content* is noteworthy. Cow's milk contains nearly four times as much ash as human milk.

Fresh milk also contains the *vitamins* which are essential for health and growth.

Origin of Constituents of Milk.—The specific constituents of milk are probably elaborated in the gland cells from certain raw materials supplied by the blood. (i) *Lactose* is derived from the *glucose* of the plasma. (a) In the lactating cow the sugar content of the blood in the mammary vein is on an average about 20 per cent. lower than that in the jugular vein[1]; no such

[1] As far as the constituents under discussion are concerned, the jugular vein blood probably resembles closely mammary artery blood.

differences can be detected in the case of dry cows. (β) Perfusion of the isolated mammary gland with Ringer's solution containing glucose results in the formation of milk containing lactose and a diminution in the glucose content of the perfusing fluid. (γ) If the mammæ are extirpated in goats, it is found that after parturition hyperglycæmia and glycosuria are present; presumably glucose is poured into the blood, but is not removed normally owing to the absence of the mammæ. (ii) *Proteins* of milk come from the *amino-acids* of the blood: the amino-acid N. is lower in the mammary than in the jugular vein during lactation. (iii) *Fat* probably comes from the *phospholipine* of the blood: there is less phospholipine and more inorganic PO_4 in the mammary than in the jugular vein. In plasma phospholipine the phosphorus–fatty acid ratio is 1–20; in milk it is 1–50; *i.e.* the mammary gland can extract the fatty acid and the PO_4 it needs from the phospholipine and still leave an excess of PO_4 in the blood leaving it.

Conditions affecting Composition of Milk.—

1. *Age.*—The milk is richest in fat in women between the ages of 20 and 35.

2. *Pregnancies.*—In a primipara the milk contains more fat and protein.

3. *Illness* reduces the total quantity of milk. If the illness is severe, the fat content falls, but the protein is raised.

4. *Menstruation.*—The menstrual flow frequently returns during lactation, but does not affect the composition of the milk in the vast majority of cases.

5. *Blood-Flow.*—The milk secretion is nearly proportional to the blood-flow to the gland.

6. *Nervous Factors.*—The quantity and even the quality of the milk may be altered by nervous impressions; fright, grief, passion, excessive sexual indulgence, may arrest the secretion, or alter its composition in such a manner as to cause it to disagree with the infant. The exact mechanism is unknown. In the cow, the secretion of fat may be almost completely arrested by even slight discomfort, but the other constituents are less affected.

7. *Diet.*—The quantity and composition of milk bear a complicated relation to the diet. (α) A *superabundant* diet does not increase the total yield or richness of the milk unless the protein content is increased (cf. γ). (β) If the diet is *inadequate*, it is found that early in lactation the body tissues are used to form milk, which is not reduced much in amount, and weight is lost; late in lactation, however, the yield of milk is reduced. (γ) An increase in the *protein* of the diet to any level regularly increases the quantity of milk secreted, usually increases the total fat yield, but there is no constant change in the protein content of the milk. A diminution in the protein of the diet to *considerably below normal* reduces the yield of milk and the fat and protein content within a few hours. (δ) Increasing the *fat* of the food above 1 grm. per kg. body weight does not increase the yield of fat; if it falls below this level in the diet the fat secretion is correspondingly diminished. (ϵ) *Lactose* secretion is not significantly affected by alterations in the diet. (ζ) A reduction of the Ca and P of the diet does not affect the yield of milk for months or even until later lactations, as the body reserves are called upon. The vitamin content of the milk depends on the amount of these substances in the diet. Alcoholic liquors like stout may serve to fatten the mother, but it is very doubtful whether they improve the quality of the milk in any way.

8. *Drugs.*—Certain drugs ingested by the mother may be excreted in the milk—(i) alcohol, if taken in large amounts; (ii) belladonna, administered in

full doses ; (iii) opium, less constantly ; (iv) iodide, bromide, and mercury, if given for a long period ; (v) saline purges, salicylates, and arsenic, occasionally.

Daily Quantities Secreted.—The following table (modified from Holt) indicates the daily quantities of milk secreted, the amount obtained by the infant at each feed, and the size of artificial feeds. It is assumed that seven feeds are given daily.

	Total Daily Quantity.	Amount Each Feed.	Artificial Feeds.
First week	10–16 oz.	½–1½ oz.	1–2 oz.
Second week	13–18 ,,		
Third week	14–24 ,,	1½–4 ,,	2½–4½ ,,
Fourth week	16–26 ,,		
Second and third month	20–34 ,,	3–5 ,,	3½–5 ,,
Four to six months	24–38 ,,	3–6 ,,	6–7 ,,
Six to nine months	30–40 ,,	Over 4 oz.	7–8 ,,

THE THYMUS

The thymus in man develops from the third branchial clefts of both sides. The two outgrowths come into contact in the middle line in front of the trachea to form a single lobed body.

Structure.—The organ consists of lobules which are bound together by connective tissue. Each lobule is made up of—

i. Outer cortex, of closely packed lymphocytes.

ii. Central medulla, which is faintly staining and consists of a reticulum of large branched cells in the meshes of which are relatively few lymphocytes. The "concentric corpuscles" of Hassall are found in this region. They consist of a hyaline centre surrounded by layers of flattened cells with poorly staining nuclei.

According to Hammar, the thymus is an ectodermal structure which later becomes invaded by lymphocytes derived from the mesoderm. He regards Hassall's corpuscles as epithelial cells which have undergone a peculiar form of differentiation. It is undecided whether any of the original epithelial elements of the thymus persist or function as secreting cells. Even those who answer these questions in the affirmative agree that the small "thymic" cells are indistinguishable histologically from lymphocytes. It is clear that if all the specific epithelial elements do disappear, the thymus can have no functions apart from those of lymphoid tissue in general.

The thymus continues to enlarge until the age of puberty, and reaches its greatest development about the fourteenth to sixteenth year. It then steadily becomes smaller, and atrophies at fifty to sixty years of age.

Extirpation.—The results of extirpation of the thymus are very conflicting. In young animals nutritive changes are said to occur. Adiposity develops, which persists for some months and passes finally into a state of cachexia and coma. The skeleton remains small and the bones are atrophic (Klose).

After castration in young animals the thymus persists and does not undergo its customary involution. It is suggested that the regression of the thymus at puberty is due to the internal secretion formed by the now mature gonads.

In any condition of malnutrition, *e.g.* in marasmus in children, and in vitamin-B deficiency, the thymus atrophies.

Hyperplasia of Thymus.—There are cases in which the thymus fails to undergo involution at the proper time or there is renewal of growth after involution has been established. In these latter cases it may attain a weight several times that of the normal organ. Such hyperplastic glands are found in infants usually unassociated with general lymphoid overgrowth ; in older individuals in connection with derangements of the organs of internal secretion, in cases of myasthenia gravis, and in status thymo-lymphaticus.

i. In infants the abnormal thymus may weigh 60 grm. at birth, and constitute an obstruction to the respiratory passages or great veins ; in older individuals it is doubtful whether mechanical obstruction is often caused by an enlarged thymus. A condition called *thymic asthma* is described, in which suffocative attacks occur which are said to be relieved by partial removal of the enlarged gland.

ii. The thymus is enlarged in 75 per cent. of cases of exophthalmic goitre and in many cases of Addison's disease, acromegaly, and eunuchoidism. In 90 per cent. of cases of myasthenia gravis the thymus forms a bulky mass. Lymphoid infiltrations are present in this condition in the skeletal muscles.

iii. **Status Thymo-Lymphaticus.**—In many young persons who have died suddenly after some slight injury or infection which seemed insufficient to cause death, general swelling of the lymphoid structures and enlargement of the thymus are often found at autopsy. The lymphoid overgrowth is, however, only part of a general constitutional inferiority of the affected person. In male subjects there is a tendency to female secondary sex characters, *e.g.* scanty hair on the face, smooth velvety skin, small external genitals, and rounded thighs. In women the thorax and extremities are slender, the genitals hypoplastic, and menstruation is irregular or absent. The musculature may be flabby, the heart is weak and soft, and the large blood vessels are relatively narrow and thin walled. The failure of this inadequate circulatory mechanism may be one of the important causes of sudden death in these subjects. There is no proof that the thymus is concerned in the production of the various clinical manifestations of status thymo-lymphaticus or in causing the sudden death which may occur. Incomplete differentiation of the sex glands is probably responsible for the failure of the thymus to undergo involution, and may also account for the other features of the condition (MacCallum).

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IV

THE BLOOD

Blood volume—Methods—Hæmorrhage—Blood grouping.
Coagulation of blood—Factors concerned—Hæmostatics—Intravascular clotting—Post operative embolism and thrombosis—Hæmophilia.
Formed elements—Red blood corpuscles—Structure of bone marrow—Stages of erythropoiesis—Fragility of red cells—Diet and red cell formation—Hæmoglobin and its derivatives—Structure of liver and spleen—Reticulo-endothelial system—Fate of red cells—Origin of bilirubin—Jaundice—Pernicious anæmia—Leucocytes—Functions—Inflammation—Blood platelets, origin, functions—Purpura.
Spleen—Size—Functions—Blood formation, destruction, reservoir—Iron metabolism—Diseases—Fat—Defence reactions—Extirpation.
Reaction of blood—Definitions—Measurement—Physico-chemical regulation—Vital reactions—Respiratory centre—Liver—Kidney—Alkalæmia and acidæmia.

The Blood Volume.—No very reliable or simple methods are available for estimating the blood volume. It appears to bear a definite relationship to the body weight. In adults the blood volume is 5 to $5\frac{1}{2}$ litres (10 to 11 pints), or one-fifteenth to one-thirteenth of the body weight.

1. The *direct methods* seek to determine the blood volume by actually collecting all the blood in the body by means of bleeding, washing out the circulation and macerating the tissues, and then determining the degree of dilution of the combined blood and washings. This was the method employed in the classical observations on decapitated animals in 1850. In animals a sample of blood is first taken and diluted a hundredfold to serve as a standard. The living animal is bled and the vessels washed out with saline, while artificial respiration and massage of the muscles are carried out to squeeze blood out of every part of the body. The muscles are then minced and extracted with saline. All the washings are collected and a sample of this mixture is diluted till it matches the standard. This method is perhaps the most reliable and may be used to control the more indirect methods. It is not free from fallacy, however: intravascular clotting may prevent some of the blood from being obtained, and myohæmoglobin may be extracted from the tissues and contribute to the tint of the washings. In this way blood volume is found to be one-thirteenth the body weight, or $5\frac{1}{2}$ litres in an adult weighing 70 kgrms.

2. Haldane's *carbon-monoxide method* depends on the power of this gas to combine with hæmoglobin and replace oxygen quantitatively. A sample of blood is first taken, and its oxygen capacity is estimated and found to be, *e.g.*, 18·5 c.cm. per cent. Oxygen mixed with a known amount of CO is breathed from a large bag until all the latter gas, *e.g.* 120 c.cm., is absorbed into the blood and combined to form carboxyhæmoglobin (COHb). A

second sample of blood is withdrawn, and the proportion of COHb is estimated colorimetrically. The technique of this latter procedure is admittedly difficult. CO replaces an equal volume of oxygen from its combination with hæmoglobin (cf. p. 341). The calculation is made as follows :

If one-seventh of the Hb is found in the form of COHb, it follows that as
18·5 c.cm. O_2 are found in 100 c.cm. of normal blood
$\frac{1}{7} \times 18{\cdot}5 = 2{\cdot}7$ c.cm. CO are found in 100 c.cm. blood after the experiment
$\therefore$ 120 c.cm. CO are found in $\frac{100}{2{\cdot}7} \times 120$ c.cm. of blood
$= 4{\cdot}5$ litres
= blood volume.

A blood volume for an adult of about 5 litres (one-fifteenth of the body weight) is obtained by this method.

This method cannot be lightly applied to sick patients, because CO prevents a proportion of their hæmoglobin from functioning properly and thus limits their supplies of oxygen further and might make their clinical condition worse. The second sample must be taken when all the CO has diffused evenly throughout the blood, and so the inhalation should continue for fifteen minutes after the absorption of the CO is complete.

3. Recently various *dye-stuffs* have been injected intravenously, and the subsequent degree of dilution employed as a method of determining the blood volume. As the dye mixes with the plasma only, a preliminary step is to find the relative volume of plasma and corpuscles. This is done by centrifuging a sample of blood in a special graduated tube or hæmatocrit, and comparing the volume of the sediment of corpuscles with that of the supernatant plasma. A dye called vital red has been used of late, 1 c.cm. of a 1 per cent. solution being injected into a vein, and after an interval a sample of blood is collected, centrifuged, and the degree of dilution of the dye in the plasma is determined. This method is easy to carry out, but the difficulty is to collect the second sample at a moment when the dye is uniformly mixed in the blood stream and none has yet escaped into the tissue spaces or urine. Unpleasant toxic symptoms have been recorded clinically following the use of this dye. The blood volume thus determined is found to be one-thirteenth body weight, or $5\frac{1}{2}$ litres.

It must be remembered that there are considerable stores of red blood corpuscles in the splenic pulp which do not circulate normally but may be pressed out in time of need (cf. p. 212).

As stated, figures varying between 10 and 11 pints are given for the blood volume, but no dogmatic conclusion is yet possible. Young animals tend to have relatively more blood than older individuals of the same species. The blood volume is kept very constant in the normal person, and it is difficult experimentally to produce any material or lasting alteration in this volume.

1. If a salt solution, whether isotonic, hypotonic, or hypertonic, is injected into the veins of a normal animal in amounts equal to 50 per cent. of the blood volume, it is found (in the dog) that half the injected fluid leaves the blood vessels in the first fifteen minutes. Most of the rest soon follows into lymph and urine, though a long time may elapse before the original volume is quite restored. Such additions of fluid are of no value to the body, and

merely hamper the respiratory function of the blood by diluting the hæmoglobin. In the case of a hypertonic solution, the osmotic pressure of the blood is raised, and consequently the first effect is to attract fluid from the tissue spaces and so further dilute the blood. A condition of hydræmic plethora results, which is transient, however, and the excess fluid is again got rid of. It is first transferred from the arterial to the venous side of the circulation with a consequent rise of venous and capillary pressure. This raises the filtering force in the capillaries which tends to drive fluid out of the vessels into the tissue spaces. At the same time the proteins of the plasma are diluted and consequently the osmotic pressure they exert is diminished. Osmotic pressure tends always to attract water, and if it is lowered the power of the blood to retain fluid is diminished and so exudation occurs. The lowered osmotic pressure of the blood enables greater filtration to occur in the glomeruli of the kidney, and large amounts of fluid are got rid of through that channel (pp. 305 and 467). The blood volume is thus adjusted to the level most appropriate for the carrying out of the body functions—*i.e.* (1) there must be an adequate concentration of hæmoglobin or oxygen-carrying power; (2) the viscosity of the blood must be suitably adjusted, because it greatly influences the resistance met with in the arterioles and consequently the level of the blood pressure; (3) the blood volume must be related to the capacity of the arterial system (Boycott).

2. If fresh blood is transfused into a normal animal, there is an immediate rise in the hæmoglobin concentration of the blood of the recipient, and in a few hours the blood volume is restored. This involves an ejection not only of the added plasma but also of a volume of the animal's own plasma equal to the bulk of injected red blood corpuscles. It is a little difficult to see what physical methods bring this adjustment about. Later, of course, the excess of red blood corpuscles is disposed of by a process of hæmolysis.

For regulation of blood volume after water-drinking and sweating, see pp. 305, 468, 470.

Hæmorrhage.—The effects of hæmorrhage depend not only on the amount of blood which is lost, but also on the rate at which this loss occurs. The compensatory powers of the body are very great, but they take time to develop their maximum effect, so that a sudden large hæmorrhage is more serious than a greater loss spread out over a more prolonged period. Following a large hæmorrhage, the blood pressure falls and the symptoms noted are mainly referable to oxygen lack. The immediate fall of *blood pressure* is due to the lowered blood volume, which diminishes the venous return and consequently lessens the output of the heart. The fall of pressure in the vessels of the head and the anæmia of the brain stimulate the vasomotor centre, and the splanchnic and cutaneous arterioles are constricted. Afferent pressor impulses also pass up the vagus to stimulate the vasomotor centre further ("vago-pressor reflex") for it is found that if both vagi are severed after severe hemorrhage a marked *fall* of blood pressure results (M'Dowall). These reactions tend to restore the blood pressure and conserve the blood in the more vital regions of the body. The spleen contracts and discharges a large number of red blood corpuscles (which were stored in the pulp) into the general circulation (cf. p. 213). Arguing from the analogy of animal experiments it may be said that a loss of 350 c.cm. of blood in an adult has no effect on the blood pressure; with the next 350 c.cm. lost, a slight but definite depressor effect

results; if the loss reaches 1750 c.cm., the fall of blood pressure is very marked and the chances of recovery become uncertain. Recovery, however, has occurred after the loss of a volume of blood equal to 3 per cent. of the body weight (over 2000 c.cm.).

The *general* symptoms of oxygen lack will be present—giddiness, faintness, and possibly loss of consciousness. The *respiratory* centre is stimulated and the breathing is rapid and shallow or " sighing " in character. The *pulse-rate* is quickened, an attempt thus being made to increase the circulation-rate and use what blood is available to greater advantage. The body temperature is subnormal.

Stages of Recovery.—The withdrawal of blood from the vessels is immediately followed by a corresponding intake of fluid from the tissues. This occurs so rapidly that in an animal bled to death from its carotid artery, the last portions of blood obtained are more dilute than the first. If the hæmorrhage occurs gradually, the inpouring of fluid into the vessels may be so marked that a bulk of blood double the blood volume may be lost in a few hours. No satisfactory physical explanation is available to account for normal blood taking up fluid from the tissue spaces. The restoration of the blood involves the fluid part first, a dilute plasma resulting. After a day or two, the specific gravity of the plasma rises, indicating that the inorganic constituents have been restored. Later still, the specific plasma proteins are regenerated. The replacement of the lost hæmoglobin depends on the proliferative powers of the red bone marrow, the effective stimulus being the oxygen lack resulting from diminished oxygen-carrying capacity. In animals, if half to two-thirds of the hæmoglobin has been lost, 2 per cent. of the total hæmoglobin and 5 per cent. of the lost hæmoglobin is restored daily, final recovery thus occurring in about three weeks or a little longer. As the normal level is approached, the stimulus of oxygen lack becomes progressively weaker, and so the process of regeneration slows down.

Repeated bleedings may double the rate of regeneration by causing hypertrophy of the red marrow. It should be noted that if the oxygen lack is very severe, as after a large hæmorrhage, the red marrow may itself be so adversely affected by the unfavourable conditions that the process of repair may be hampered.

Nucleated red cells may appear in the circulating blood, as well as immature cells (reticulocytes) or badly shaped forms (poikilocytosis). Many small red corpuscles are found, tending to make the average size of the red cells lower than normal. The cells may be deficient in hæmoglobin, or stain diffusely with basic dyes (polychromatophilia), or show deeply staining basic dots (basophil punctuation) (cf. p. 194).

In man the full restoration of the blood volume takes some days, and the process is greatly facilitated if a sufficient bulk of fluid can be spared from the tissue spaces. Free drinking of water is therefore of great value, and in the dog it has been found that placing water in the stomach speeds up the recovery process from a period of days to one of hours. In cases of emergency, however, it becomes necessary to introduce fluid into the vessels so as to maintain an effective circulation.

1. *Saline* injected intravenously, though it temporarily replaces the lost fluid, is very rapidly eliminated, because it dilutes the proteins of the plasma (cf. p. 180). Fluid absorbed from the skin and bowel appears to be retained

longer, and is more beneficial in the long-run. The reason for this is not clear unless it is assumed that the fluid is absorbed together with a certain amount of colloid. The colloids of the plasma antagonize the capillary blood pressure (which tends to filter fluid outwards), and thus the plasma proteins tend to maintain the fluid content of the blood.

2. To overcome the objections to ordinary saline, *gum saline* was employed during the war. Seven per cent. gum acacia, consisting of mucilage of acacia (B.P.) diluted five times and the excess of calcium removed, and 6 per cent. gelatin heated to 100° C. may be employed. The gelatin solution is dangerous, because it cannot be guaranteed to be free from the presence of the spores of *Bacillus tetani*. The gum is of value in two ways : (i) it exerts an osmotic pressure and thus tends to retain the saline in the vessels ; (ii) it possess about the same viscosity as blood, and it can be easily shown that the more viscous a fluid is, the greater is the frictional resistance it meets in the arterioles, and consequently the blood pressure is better maintained.

3. The ideal method, however, is *blood-transfusion*, which provides a fluid of the right viscosity and osmotic pressure, and further restores the oxygen-carrying capacity of the blood to its normal level. Two precautions must be observed : the blood must be kept fluid, *i.e.* coagulation must be prevented (p. 187) ; and the compatibility of the offered red blood corpuscles must first be determined. If foreign red cells of an unsuitable nature are injected, very serious symptoms and even death may ensue. During the actual injection the patient may complain of pain. The red cells are first clumped and then undergo hæmolysis ; the resulting hæmoglobin is partly excreted in the urine, and partly broken down to form much bilirubin, and thus intense *jaundice* appears (cf. p. 203). The hæmoglobin which is passed out in the glomeruli is precipitated in the tubules possibly as acid hæmatin, owing to the filtrate becoming acid as it passes down the tubule ; the lumen of the tubules is obstructed and the flow of urine is seriously interfered with.

In spite of alleviative measures such as injections of saline, cupping of the loins, etc., almost complete *anuria* may develop in consequence, and nc more than a few ounces of albuminous urine be passed daily. The nitrogenous constituents of the blood rise, and a condition of latent uræmia results (*q.v.*). The patient in severe cases dies in eight to ten days after developing increasing lethargy and coma.

It has been found that people can be divided into four groups according to the behaviour of their red cells. It should first be noted that in a blood transfusion the *serum* of the donor can be ignored. It is so diluted by the serum of the recipient that it can exert no action. We need therefore only consider the corpuscles of the donor and the serum of the recipient in respect of their effects upon one another. A drop of the donor's blood is received in 1 c.cm. of 1·5 per cent. sodium citrate solution to prevent coagulation. One drop of the resulting suspension of the *donor's corpuscles* is taken and mixed on a microscope slide with one drop of the *recipient's serum*. The specimen is examined after a few minutes : if the red cells have become clumped or agglutinated, the bloods are incompatible. This is the direct method, and is the most reliable one we possess. By testing a large series of bloods the following table can be constructed (+ signifies agglutination, and therefore incompatibility ; — means that the red cells are unaffected and are therefore suitable) :

DONOR'S CORPUSCLES

	Group I.	Group II.	Group III.	Group IV.
Recipient's serum—				
Group I. . .	−	−	−	−
,, II. . .	+	−	+	−
,, III. . .	+	+	−	−
,, IV. . .	+	+	+	−

The table can readily be constructed for one's self if the following facts are remembered. Group I. are the *universal recipients*; they can receive any human red cells without ill effect. In the table it will thus be found that if cells of I., II., III., or IV. are given to a recipient of group I., no agglutination occurs. Group IV. are the *universal donors*; they can be administered safely to members of all the other groups. Looking at column IV. it is seen that the cells are given to groups I., II., III., or IV. without harm. Finally, groups II. and III. can receive red cells of group IV. and of their own group as well. If sera of groups II. and III. are kept in stock, any red cells can be assigned to their respective group. To appreciate this, examine the second and third lines of the table. Thus cells of group I. will be agglutinated by both stock sera; cells of group II. by serum of III. only; cells of group III. by serum of II. only; while cells of group IV. are agglutinated by neither sera II. or III. This method is not absolutely reliable, because some cells appear to belong to an unclassifiable group.

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Coagulation of Blood.—Coagulation of blood after it is shed depends on the interaction of *thrombin* with the soluble *fibrinogen* of the plasma to form an insoluble protein—*fibrin*. Thrombin is not found in the circulating blood but is formed when blood is shed from an inactive precursor *prothrombin* (*thrombogen*) in the presence of (i) free *calcium* ions and (ii) a substance of a phospholipine nature—*cephaline* (Howell), *thrombokinase* (Morawitz)—which is liberated from the disintegrated blood platelets or the damaged tissue cells. Much light has been thrown on this very complex problem by attempts which have been made to obtain the various interacting substances in relatively pure form.

Fibrinogen. Blood is withdrawn from a blood vessel into a receptacle containing potassium oxalate (to 0.1 per cent.), which prevents coagulation by removal of the free calcium ions owing to the formation of a precipitate of insoluble calcium oxalate. The blood is centrifuged and the supernatant plasma (*oxalate plasma*) is removed. To it is added an equal volume of a saturated solution of NaCl: a precipitate of fibrinogen is formed which may be redissolved in distilled water. It coagulates on heating to 60° C.

The fibrinogen of the plasma is probably formed by the liver (cf. p. 400).

Thrombin. —*Preparation.*—Fibrin is treated with 8 per cent. NaCl at a low temperature for several days. The extract is filtered; the filtrate

contains dissolved protein, but is rich in thrombin. By repeatedly shaking the filtrate with $CHCl_3$ the dissolved proteins are removed and thrombin is left in a fairly pure state (Howell).

Properties.—(i) It is of a protein nature : it gives the biuret test, and positive reactions for tryptophane and histidine ; (ii) it is readily soluble in water ; (iii) it is *not* present in the circulating blood, so it must be formed after the blood is shed ; (iv) when thrombin is added to oxalate plasma the fibrinogen is converted into fibrin and a clot is formed. This experiment proves that calcium ions are not necessary for the thrombin-fibrinogen interaction, and that these ions must play their part at an earlier stage (in the conversion of prothrombin into thrombin ; (v) it is *not* an enzyme, for (*a*) salt-free solutions of thrombin are not destroyed on boiling, (*b*) it reacts with fibrinogen in a quantitative manner : the amount of fibrin formed is directly proportional to the amount of thrombin present ; (vi) the mode of action of thrombin is obscure ; there is no definite evidence that it forms an integral part of the fibrin molecule, so that one cannot confidently assert that it unites chemically with fibrinogen. It is suggested that thrombin behaves like an " agglutinin " : it is absorbed by the fibrinogen particles and confers on them an adhesiveness which causes them to fuse together first as fine needles and then as threads. These fibrin threads entangle red blood corpuscles and contract to form the clot ; clear yellow fluid—*blood serum*—is squeezed out ; (vii) the inactive precursor of thrombin—prothrombin—can be demonstrated in the circulating blood.

Prothrombin (Thrombogen)—*Preparation.*—An equal volume of acetone is added to oxalate plasma ; a precipitate is formed which is filtered off, washed with ether, spread out on filter paper, and dried. If extracted with water, a solution is obtained which contains prothrombin (Howell).

Properties.—(i) It is a globulin or pseudo-globulin which can be precipitated by 35 to 50 per cent. ammonium sulphate ; (ii) if added alone to a fibrinogen solution it does not cause clotting ; but if calcium ions are also added in appropriate concentration, clotting promptly occurs. According to Howell, *calcium ions activate prothrombin directly*, the maximal effect being obtained in 3 to 6 minutes ; (but of course one cannot be certain that the prothrombin used is perfectly pure and is not contaminated by other substances). It is also claimed that ethyl alcohol, chloroform ($CHCl_3$), carbon tetrachloride (CCl_4), can also activate prothrombin, and this change may occur spontaneously in water. If we accept the work of Howell, then as calcium ions and prothrombin are present in the circulating blood, it follows that intravascular clotting must be prevented by some inhibitory substance, which, according to Howell, is *heparin* (*v. infra*).

Heparin[1] (*anti-prothrombin*) has been obtained from the liver and other organs and is present in the circulating blood. The purified preparation is water-soluble, non-toxic, thermostable, and gives no protein reactions ; it is believed to consist of a *carbohydrate* and *glycuronic acid*. One mg. of heparin prevents the coagulation of upwards of 40 c.cm. of shed blood for 24 hours. If added to a solution of thrombin, or incubated with it for many hours, it does not interfere with the coagulating effect of thrombin on fibrinogen ; it is therefore not a direct antithrombin. It is suggested by

[1] Howell and Holt, *Amer. Journ. Physiol.*, 1918, vol. xlvii. p. 328 ; *ibid.* 1922, vol. lxiii. p. 434 ; 1924–5, vol. lxxi. p. 553.

Howell that heparin combines or reacts with prothrombin to prevent its activation to thrombin.

Phospholipine factor (*Cephaline, thromboplastin, thrombokinase*).—The addition of extracts of tissues or of platelets greatly accelerates the process of clotting in shed blood. This is particularly well seen in the blood of birds, reptiles, and fishes: if such blood is collected in a clean tube and promptly centrifuged the supernatant plasma may not clot for hours or not at all; but if tissue extracts are added clotting occurs in a few minutes. The active principle in tissue extracts is soluble in ether and alcohol and is of a lipoid character; it has been presumed to be lecithine, but according to Howell it is the closely related compound *cephaline* [1] in which the nitrogenous base is not choline but amino-ethyl alcohol $CH_2OH.CH_2NH_2$.

When blood comes into contact with a foreign surface, the platelets agglutinate, imbibe water, and disintegrate; in this way cephaline [2] is liberated and initiates the process of coagulation. Its mode of action is unsettled: it definitely does not unite with prothrombin to form thrombin, because purified thrombin does not contain more than a trace of phosphorus. As stated above, Howell claims that calcium can activate prothrombin directly without the intervention of any other substance; he believes that the cephaline formed when blood is shed neutralizes the inhibitory substance—heparin—which is normally present in the circulation and which prevents the spontaneous coagulation of the blood in the body. The calcium prothrombin reaction can then take place, thrombin is formed and clotting occurs.

Prothrombin + Ca ions = Thrombin

↙

normally inhibited by Heparin.

When blood is shed Heparin is neutralized by Cephaline from platelets.

Thrombin + Fibrinogen = Fibrin.

Anti-Thrombin.—(1) Traces of an anti-thrombin can be demonstrated in the circulating blood. It probably serves to neutralize any trace of thrombin which may be formed in the blood stream as a result of the disintegration of the formed elements of the blood.

2. *Hirudin*, obtained from the salivary glands of the leech, is a proteose which can neutralize the action of fully-formed thrombin; it is thermostable, unlike blood anti-thrombin which is destroyed at 70° C. Hirudin acts equally well in vitro and in vivo.

3. The injection of *peptone* (0·3 grm. per kg.) intravenously into a fasting animal produces a fall of blood pressure, coma, and an incoagulable condition of the blood. Peptone only produces this last effect in vivo; it probably causes the formation of excessive amounts of antithrombin.

Hæmostatics.—The hæmostatics which precipitate blood plasma, such as alum or ferric chloride, have a low efficacy, as the coagula formed are loose

[1] Before the identity of this substance was established it was called *thrombokinase* (Morawitz), but there is no evidence that it is a kinase or enzyme.

[2] In the tissues and platelets cephaline appears to exist united with protein. If tissue extracts are heated to 60° C. the protein-cephaline complex is coagulated and its thromboplastic action is injured or destroyed.

in texture and permit the escape of blood from the damaged vessels. Commercial hæmostatics consisting of tissue extracts, platelets, cephaline, horse serum, thrombin, have been tested[1]; they are all effective in vitro at 37·5° C.; some are effective at room temperature too. A *hot* bandage soaked in these coagulant hæmostatics should be applied to the bleeding part; this is more effective than continuous irrigation with the hæmostatic, in which case the clots formed are disturbed by the moving liquid. Some of these hæmostatics when injected in appropriate concentration, intravenously or intramuscularly, definitely shorten the clotting time of the blood without risk of intravascular clotting or serious alteration of blood pressure, and they appear to be of value in the treatment of internal hæmorrhage.

Coagulation may be prevented or delayed as follows:

1. Prevent the blood from coming into contact with foreign particles or broken down tissues, or rapidly cool blood to 0° C., which prevents the platelets and corpuscles from disintegrating, *i.e.* delay the formation of cephaline (p. 186).

2. Remove free calcium ions from the solution—(i) by the addition of potassium oxalate, which precipitates an insoluble calcium oxalate; (ii) addition of sodium citrate—this does not precipitate calcium; but the calcium is bound with the citrate radicle and is no longer present in the ionized form.

3. Use of animal substances: (i) hirudin; (ii) peptone (p. 186).

4. Addition of neutral salts, *e.g.* half saturated Na_2SO_4. This dilutes the blood and apparently impedes the interaction of the various substances concerned in clotting.

Intravascular Clotting.—1. Injection of thrombin into the circulation does not produce clotting owing to formation of antibodies.

2. Injection of tissue extracts in small amounts may produce one of two effects: (i) extensive intravascular clotting; (ii) an incoagulable state of the blood owing to over-compensation, *i.e.* over-formation of antibodies.

3. Slowing down of the circulation and damage to the endothelial lining of the blood vessels tend to produce intravascular clotting. Thrombi appear on atheromatous patches in the arteries or on damaged valves in the heart; the process begins with the deposition on the walls of the blood channel of masses of platelets to which the passing leucocytes become adherent. Local formation of thromboplastic substance (cephaline) occurs and a fibrin network is formed which entangles the red blood corpuscles. In hearts which have suffered from auricular fibrillation, the virtual paralysis of the auricles and the consequent stagnation of blood within them often results in the formation of clots in the auricular appendices. As long as the blood stream is very weak and slow the clots do not shift their position. Should rhythmic co-ordinated contraction of the auricle be restored (*e.g.* by quinidine, p. 277), the clot may be shifted and plug a vessel in the lungs, brain, or elsewhere.

Post-Operative Embolism and Thrombosis.—After surgical operations, in a small proportion of cases, emboli consisting of small particles of clot are liberated, which usually settle in and obstruct the pulmonary vessels, producing a condition called infarction of the lungs. Sometimes the cerebral and very rarely the coronary arteries are affected. The infarction of the lungs may lead (i) to instantaneous death (the cause of which is not very

[1] Pickering and Hemingway, *Brit. Med. Journ.*, 1926, vol. i. p. 1029.

clear except when a large branch of the pulmonary artery is involved, throwing a great strain on the right ventricle); (ii) death after a few minutes or hours during which time intense dyspnœa and pain in the chest are prominent symptoms (for cause of dyspnœa, see p. 371); (iii) recovery may occur with signs of consolidation of the lungs. There is rarely any evidence of the source of the particles of clot. If a thrombus is found, it is usually at the junction of the internal and external iliac veins. The thrombus may appear on the opposite side of the body to that on which the operation was performed. There is no sound evidence that the clotting spreads directly from the operation area to the main thrombus. Abdominal and pelvic operations are particularly liable to be followed by this complication.

Factors.—1. The circulation in the veins of the trunk and legs is sluggish because of the enforced lack of movement of the muscles. Embolism is rare after operations on the upper limbs, as the patients are not kept so quiet.

2. Cephaline may be liberated in the damaged tissues of the operation area, pass in the lymph stream to the relatively stagnant column of blood in the great veins and produce clotting.

3. The veins may have been bruised during the operation liberating cephaline locally.

4. A mild grade of sepsis may damage the vein wall.

Hæmophilia is an inherited anomaly usually transmitted by females who themselves show no symptoms, to males who manifest signs of the disease. The condition is characterized by a marked increase in the coagulation time of the blood (normal 5–10 minutes), and a tendency to severe bleeding after injuries of any kind, even of the most trivial character. There is no deficiency of plasma constituents, *e.g.* platelets, fibrinogen, or calcium salts. According to Howell, the delayed clotting in hæmophilia is due to exceptional *stability* of the platelets, and consequently defective cephaline formation when the blood is shed. Normal blood kept in a paraffin vial remains fluid for fifty minutes; after thirty minutes most of the platelets have agglutinated and are commencing to disintegrate. Hæmophiliac blood under the same conditions remains fluid for five hours; after thirty minutes the number of intact platelets has only fallen from 326,000 to 280,000 per c.mm., and after two hours to 36,000.[1]

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Formed Elements.—The formed elements of the blood are—

(*a*) The red blood corpuscles.
(*b*) The various forms of white blood corpuscles.
(*c*) The blood platelets.

Development

Red Blood Corpuscles. As a result of the work of Doan, Cunningham, and Sabin, it may be stated with fair confidence that in mammals and birds,

[1] Dr. Pickering informs me (unpublished) that platelets from a case of hæmophilia disintegrate as rapidly as normal *after washing with isotonic saline*. He suggests the platelets in this disease are enclosed by a film of stable plasma which protects them from breaking down.

both in the embryo and in extra-uterine life, the red blood corpuscles develop *intravascularly* from the endothelial lining of minute blood vessels; the white corpuscles develop extra-vascularly and pass actively through the lining wall of the capillaries into the circulation.

1. In the *early embryo*, blood formation takes place first in the mesoderm of the yolk sac, and later in the body of the fœtus. The region in the yolk sac where the process commences is termed the area vasculosa. The mesoderm consists originally of a syncytium or nucleated mass of protoplasm with indefinite cell outlines. Fluid droplets appear and run together, and thus part of this area is hollowed out to form a network of capillary blood vessels; the remains of the protoplasm persist as the endothelial lining. Some of these endothelial cells round off, develop hæmoglobin in their interior, and become primitive nucleated red corpuscles or *megaloblasts*. Sabin has observed in the living chick embryo the actual division of the endothelial cells of the newly formed vessels to form in places masses of hæmoglobin-bearing cells or blood islands (Fig. 55). The megaloblasts multiply in the blood stream, giving rise to further generations of smaller nucleated red cells and finally to non-nucleated discs. The nucleated red cells disappear from the blood by the middle of fœtal life. The white corpuscles develop at a later date extra-vascularly from mesoderm cells, and then find their way into adjacent blood vessels.

2. From the *middle of fœtal life* to about one month before birth the liver and spleen are important sites of blood formation, and the blood spaces of these organs are full of nucleated red cells; the corpuscles are derived from the endothelial lining of the blood channels in these organs. It is noteworthy that in babies, the subjects of congenital syphilis, the liver at birth still presents this fœtal appearance. In times of emergency the liver and spleen may resume this blood-forming function.

3. At about the middle of fœtal life the *bone marrow* begins to function as a blood-forming organ, and is normally the sole region where red cells and granular leucocytes are formed after birth.

Structure of Bone Marrow.—Bone marrow consists of fat cells, blood vessels, and a minimal framework of reticulum and reticular cells; these are the only elements found in yellow marrow, but in red marrow numerous blood cells and their precursors are present too. At birth the shafts of the long bones are uniformly pink; microscopically the fat cells are inconspicuous and the blood cells predominate. At puberty, the middle of the shaft (*e.g.* of the femur) becomes fatty and this change extends till red marrow is only found as a small patch at the upper end of the diaphysis. The epiphyses of the long bones in the adult become almost wholly fatty too, and so do the bones of the carpus and tarsus (Piney [1]). Red marrow persists throughout life in the vertebræ, sternum, ribs, and bones of the skull and pelvis. If signs of diminished marrow activity are looked for, a rib or a vertebra should be examined; the shaft of the femur is studied if evidence of extension of hæmatopoiesis [2] is sought.

Vascular Arrangement.—The nutrient artery of the bone breaks up

[1] *British Medical Journal*, 1922, ii. 792.

[2] *Hæmatopoiesis*=formation of blood cells; *granulopoiesis*=formation of white blood cells; *erythropoiesis*=formation of red blood cells; *myeloid* cells=white blood cells and their precursors.

into smaller branches, which finally lead to a network of *sinusoids*. These are thin-walled vessels with the capacity of large veins, but lined with a thin endothelium like that of the capillaries. Because of their large cross-section the blood flow through them is sluggish, and consequently the oxy-hæmoglobin becomes extensively reduced; the low oxygen tension in the

FIG. 55.—Development of Red Blood Cells in Chick Embryo.

B.i. = Blood island (clump of nucleated red cells in newly formed blood vessel); L. = Lumen of vessel; A. = Mesodermal cells undergoing liquefaction; En. = Endoderm; Mes. = Mesoderm; C. = Cœlom. (Sabin.)

marrow stimulates erythropoiesis (cf. p. 182). Many of the sinusoids, however, are under normal conditions completely collapsed and quite impermeable to blood; they can only be demonstrated when the cellular elements of the marrow have been destroyed (p. 191). The injection of Indian ink into the nutrient artery then reveals these vessels as minute black streaks lined by very thin endothelial cells which are visible between every one

or two fat cells (Doan) (Fig. 56); these collapsed sinusoids are the site of erythropoiesis. Normal red marrow contains many types of cells which are so closely crowded together that a study of their inter-relationship is very difficult. The marrow must be artificially simplified before interpretation of the microscopic appearances is possible.

If a *pigeon* is starved for 10 to 17 days all the cellular elements disappear from the red marrow, which now resembles normal yellow marrow. Feeding is then resumed; within 24 hours the fat begins to be mobilized and in 48 hours it has almost completely disappeared from the marrow. The

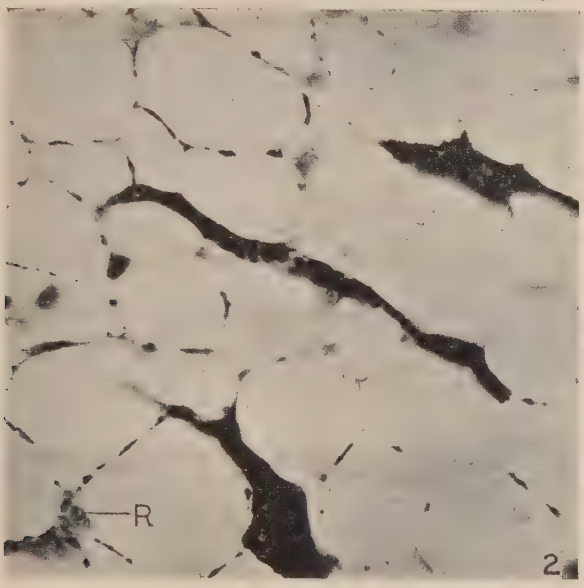


FIG. 56.—Section of Hypoplastic Bone Marrow (Pigeon) injected with Indian Ink. Three venous sinuses are filled with the injection mass; extending between them are collapsed intersinusoidal capillaries marked by fine lines of particles of carbon between double rows of excessively thin endothelial cells. Capillaries join sinuses by definite conical openings. R=reticular cell. (Doan, Cunningham, and Sabin.)

single large globule in the fat cells breaks up into many small droplets, which pass out towards the patent sinusoids, leaving branched cytoplasmic processes behind. One may perhaps compare the behaviour of the fat with that of cerebro-spinal fluid; the fat is removed when hæmatopoiesis is about to take place, and it accumulates in the marrow when the cellular elements are reduced. The place of the fat is first taken by a curious *gelatinous* material, which fills all the spaces left between the shrunken fat cells. The source and nature of this gelatinous material are unknown, but its deposition precedes the phase of erythropoiesis, which in its turn precedes granulopoiesis and so can be studied separately. In the *rabbit* a different procedure is adopted. Killed typhoid bacilli are injected at intervals of

(Figs. 1–4, 6–8, 10–12.—Cells taken from Marrow of Living Animal (rabbit) by puncture and stained with neutral red and janus green. Fig. 9 is from human blood.)

Fig. 1.—*Megaloblast.* Faintest trace of hæmoglobin visible in cytoplasm in living state. Large mitochondria in cytoplasm (green), both rod-like and coccoid, but no bodies that react to neutral red.

Fig. 2.—Maturing *Erythroblast.* Concentration of chromatin at nodes of nuclear network. Mitochondria concentrated on one side of nucleus.

Fig. 3.—Mature Erythroblast. Mitochondria fewer; almost full complement of hæmoglobin.

Fig. 4. Normoblast. Nucleus is pyknotic and ready for extrusion (cf. Fig. 57). Very scanty mitochondria.

Fig. 5.—Red Cell for comparison.

Fig. 6.—Reticular Cell of Hypoplastic Bone Marrow (hæmatoxylin and eosin), showing Mitosis (cf. Fig. 56).

Fig. 7.—Primitive White Cell. Very limited cytoplasm containing mitochondria.

Fig. 8.—Primitive White Cell; more mitochondria.

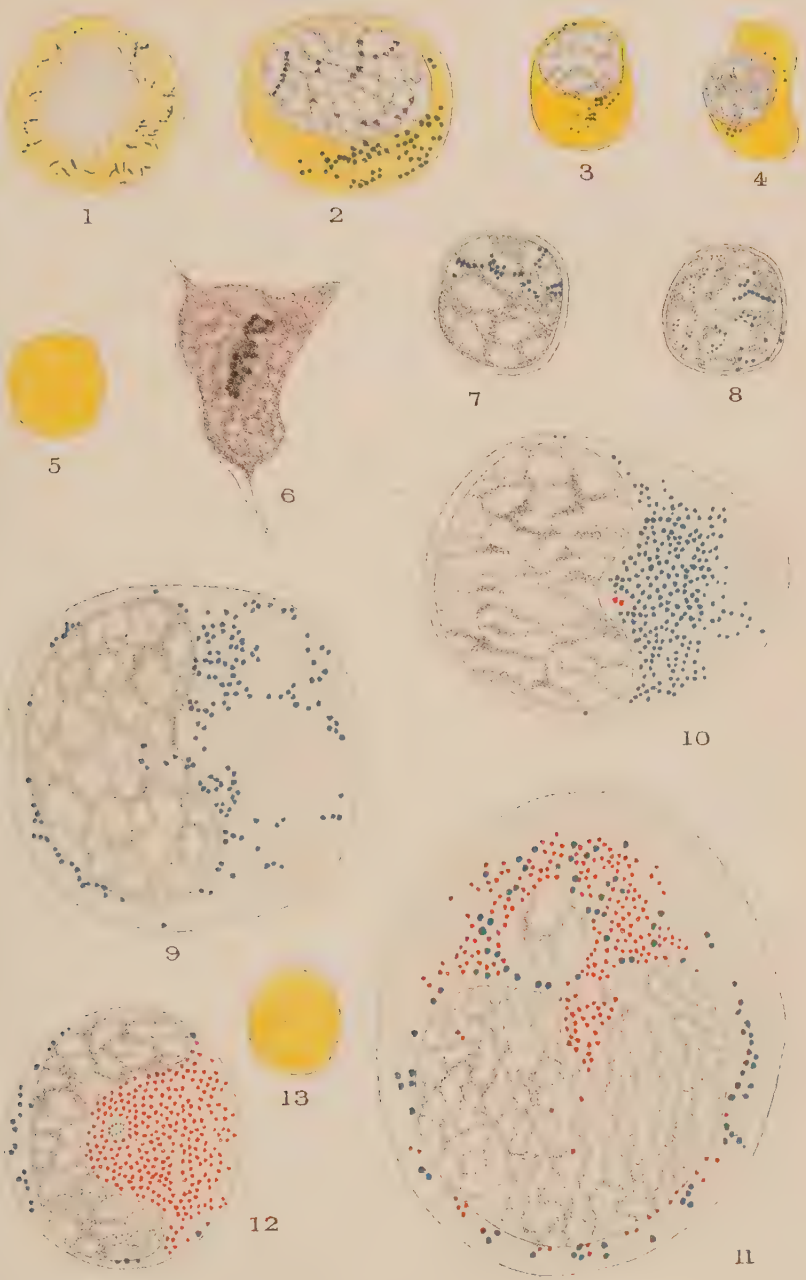
Fig. 9.—Myeloblast (human blood). Bean-shaped nucleus, more cytoplasm and mitochondria.

Fig. 10.—Myelocyte, Type A. First appearance of granules which stain with neutral red (these are probably the specific granules of the granulocytes).

Fig. 11. Myelocyte, Type B. Neutral red granules are greatly increased in number and have become dispersed among the mitochondria, which are diminished in number.

Fig. 12. - Myelocyte, Type C. Mitochondria are few in number and are only found round the convex surface of the nucleus. The concavity of the nucleus is entirely filled with neutral red granules.

Fig. 13. Red Cell. (Doan, Cunningham, and Sabin, *Contribution to Embryology*, Carnegie Publications, 1925.)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two days for 6 to 8 days ; this results in the disappearance of all the myeloid elements and again erythropoiesis alone can be studied. The red marrow may further be stimulated to activity by hæmorrhage, or reduced to a quiescent condition by the transfusion of blood from a suitable donor.

Stages of Erythropoiesis.—In the following account the description of Doan, Cunningham, and Sabin [1] has been followed and their terminology has been adopted.

1. Many of the marrow sinusoids which were previously patent become collapsed ; the blood flow through the marrow is diminished and this intensifies the anoxæmia which favours erythropoiesis.

2. The endothelial lining of the collapsed capillaries becomes swollen and the cells divide repeatedly to give rise to various immature red cells which fill the sinus completely. The young cells lie nearest to the lining of the sinus and the more mature cells lie in the centre.

The cells in the order of their development are named *megaloblasts*, *erythroblasts* (early and late) *normoblasts*, young red cells or *reticulocytes*, mature red blood cells (*erythrocytes*) (Sabin). The lining membranes of the immature cells are "sticky," [2] so that the cells adhere to one another, forming a solid mass. As the cells mature their membrane is altered so that the corpuscles begin to separate one from the other. The plasma then begins to percolate between the cells, and finally they are swept out of the erythropoietic capillaries into the veins of the marrow, and so into the general circulation.

Of the erythroid cells in normal marrow 70 per cent. are normoblasts, about 26 to 29 per cent. are late erythroblasts, early erythroblasts form 1 to 4 per cent., while megaloblasts are very scanty. The marrow thus contains a large store of cells which are almost ready for delivery as need arises. The cytology of the erythroid cells must now be described [3] (see Plate, Figs. 1–5).

(*a*) Megaloblast (Plate, opposite p. 192).—This cell is directly formed from the endothelium. It is a large cell, with a large vesicular nucleus, well-marked nucleolus, and scanty chromatin. The cytoplasm contains numerous rod-like mitochondria ; hæmoglobin can be detected in fresh preparations, but in films stained with basic dyes, the basophil reaction of the cytoplasm obscures the acidophil hæmoglobin. Stained with cresyl blue well-marked reticulation of the cytoplasm is apparent. This type of cell is rarely seen in normal marrow, but is characteristic of the marrow of pernicious anæmia.

(*b*) Erythroblasts (early and late) (Plate, Figs. 2 and 3).—The megaloblast enlarges in size ; the nucleus is large relative to the amount of cytoplasm and shows a fine chromatin network. The mitochondria become round and tend to be grouped round the nucleus. These *early* erythroblasts divide to give rise to smaller *late* erythroblasts, with an eccentric nucleus, dense chromatin network, fewer mitochondria, and more hæmoglobin.

(*c*) Normoblast (see Fig. 57).—The mitochondria are disappearing ; the

[1] Doan, Cunningham, and Sabin, *Contribution to Embryology*, Carnegie Publications, 1925, vol. xvi. p. 163.

[2] Key, *Arch. Int. Med.*, 1921, vol. xxviii. p. 459.

[3] The living marrow cells may be stained (vital staining) with Janus green and neutral red—the former stains the mitochondria and the latter the cell granules (see Plate). Fixed sections are stained with eosinate of methylene blue (Jenner or Leishman's stain), to show nuclear details and the basophilia or acidophilia of the cytoplasm. Living cells are stained with cresyl blue to bring out the *reticulation* in the cytoplasm (Fig. 57).

nucleus is deeply stained with basic dyes and shows no chromatin network (pyknosis). This pyknosis is a sign of degeneration and the nucleus is soon extruded, a young red cell or reticulocyte being formed. The nucleus may assume bizarre shapes or break up into fragments before it finally disappears.

(*d*) Reticulocyte.—The young red cell is so called because on vital staining with cresyl blue a network is apparent in the cytoplasm; the reticulum is visible as a heavy wreath or ball, or clumps of small dots, or a faint thread between two small nodes (see Fig. 57). At birth 30 to 50 per cent. of the red cells in the circulation are reticulated, but their number drops during the first week to less than 1 per cent., at which level it remains throughout life. Their number is increased whenever red cells are being

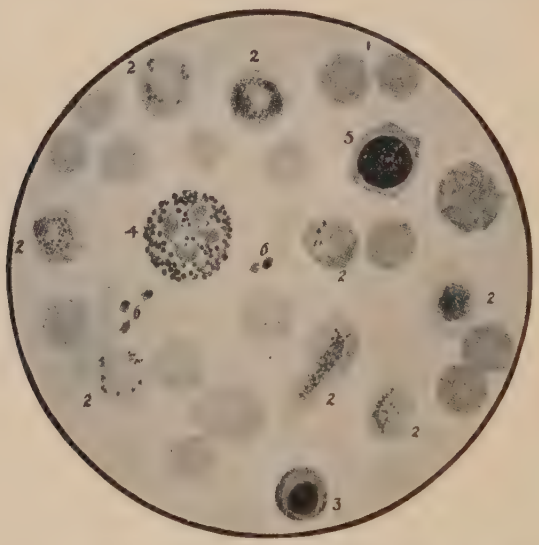


Fig. 57.—Film of Blood stained with Cresyl Blue to show Reticulation of Cytoplasm.

1. Normal red cells; 2. Different kinds of reticulocytes (note the different forms which the reticulum takes); 3. Normoblast with deeply staining (pyknotic) nucleus and some reticulum at the periphery; 4. Eosinophil leucocyte (note lobed nucleus and coarse granules) 5. Lymphocyte; 6. Blood platelets. (Krumbhaar, in Cowdry's *Special Cytology*, 1928, vol. i. p. 305.)

rapidly manufactured; for example, if hæmolytic poisons are injected intravenously to destroy the circulating red cells, the marrow proliferates and numerous young red cells pass into the blood stream. It is then found that 25 to 35 per cent. of the circulating red cells are reticulocytes (cf. pp. 182, 205).

Polychromatophilia is a condition in which the erythrocytes take diffusely some of the basophil as well as the acidophil stain; it is probably a sign of immaturity of the cell. It is believed that the reticulum which is brought out by vital staining is an artificial clumping of the same substance that with Leishman's methods stains diffusely as polychromatophilia (Krumbhaar).

Basophil Punctation of the red cells is characteristic of lead

poisoning ; the granules are probably cytoplasmic structures and not nuclear fragments, for they may be present in cells with intact nuclei.

Poikilocytosis is a term used to describe abnormalities in the shape or the size of the red cells.

Normal Red Cells are circular, non-nucleated biconcave discs. The nature of their internal structure is still undecided. They are possibly lined by a lipoid membrane within which is a stroma containing hæmoglobin in its interstices. The average diameter of the red cells in health is 7·3μ, the range of size being from 5·5μ to 8·8μ. In pernicious anæmia the average size is *greater* (about 8μ), and the range is from 4μ to 12μ (Price Jones). If the H ion concentration of the blood rises, the size of the corpuscles increases. The normal number of red cells is 4·5 to 5·5 million per c.mm. The amount of hæmoglobin per 100 c.cm. of blood in normal persons is variously given between 13·8 and 15·6 grm. The term "100 per cent. hæmoglobin" is meaningless unless the standard employed is known ; "100 per cent. hæmoglobin" on Haldane's hæmoglobinometer represents 13·8 grm. Hb per 100 c.cm. blood ; the standard is regarded as too low by American workers. It must be remembered that 1 grm. of Hb when fully saturated can combine with 1·34 c.cm. oxygen, so that the hæmoglobin percentage is an index of the oxygen-carrying power of the blood. At birth the number of red cells and the hæmoglobin percentage are high. Both diminish steadily, especially the hæmoglobin, which at the end of the first year is well below the normal average ; recovery then gradually takes place (see Fig. 59).

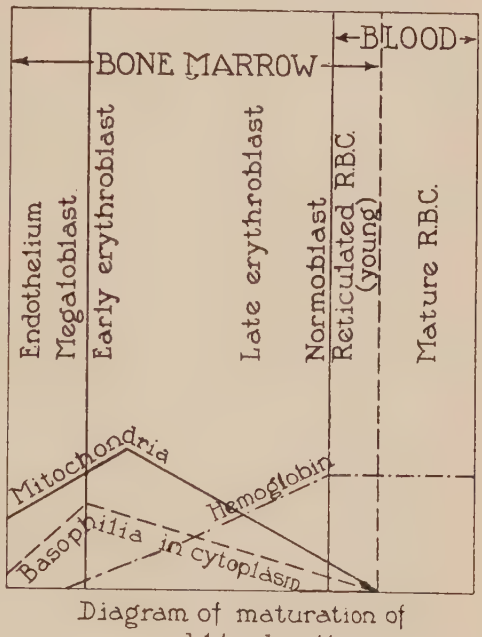


Fig. 58.—Chart showing Stages in Development of Red Blood Corpuscles. (Sabin, *Physiol. Rev.*, 1928, vol. viii. p. 225).

Colour Index is a term used to express the average hæmoglobin content of the corpuscles of a given blood. It is obtained by dividing the percentage of hæmoglobin by the percentage red cells (5 million per c.mm. being taken as 100 per cent.). Thus a blood with a hæmoglobin per cent. of 60 and a red count of 2·5 millions (=50 per cent.) has a colour index of $\frac{60}{50}=1{\cdot}2$. In secondary anæmia the colour index is considerably below 1, in pernicious anæmia it is about 1 or over owing to the presence in the blood of many large red cells (cf. p. 204).

Fragility of the Red Corpuscles.—Red cells can remain for hours in

isotonic salt solution without damage, but in distilled water they are quickly hæmolysed. Owing to the higher osmotic pressure inside the cell, fluid is attracted into the corpuscle until it bursts and its hæmoglobin is liberated. The *fragility* of red cells is determined as follows: A drop of blood is added to a series of tubes, each containing 1 c.cm. of different strengths of hypotonic salt solution varying from 0·7 to 0·25 per cent. Each tube is shaken and allowed to stand for two hours at room temperature. If no hæmolysis occurs, the unchanged corpuscles are found at the bottom of the tube, overlaid with the colourless salt solution. If hæmolysis takes place, a transparent red solution results. Normally hæmolysis begins at 0·45 per cent. and is complete at 0·35 per cent. In *acholuric jaundice* (p. 217) the corpuscles are excessively fragile, and hæmolysis may begin as high as 0·7 per cent. and be complete at 0·45 per cent. In most other anæmias, the resistance is *increased*, depending on the severity of the anæmia. Hæmolysis may then not begin until 0·36 per cent. and not be complete before 0·24 per cent. After splenectomy also (p. 216) the resistance of the red cells increases.

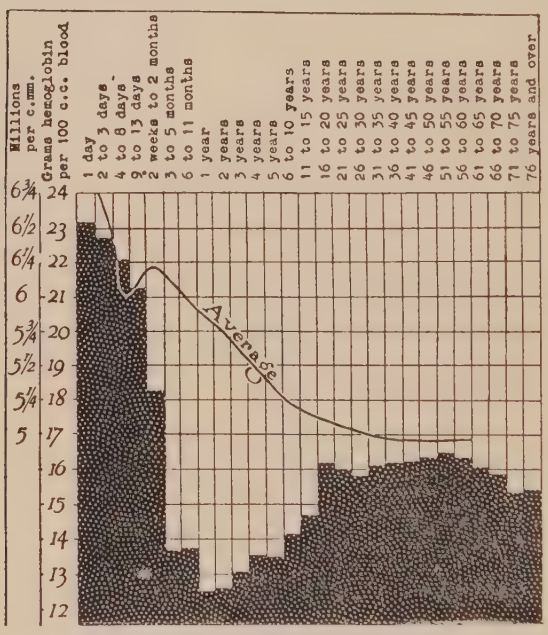


Fig. 59.—Changes in Blood with Age.

Black areas show hæmoglobin content of blood in grms. per 100 c.cm. Continuous line shows red blood count in millions per c.mm.—After Krumbhaar, in Cowdry's *Special Cytology*, 1928.

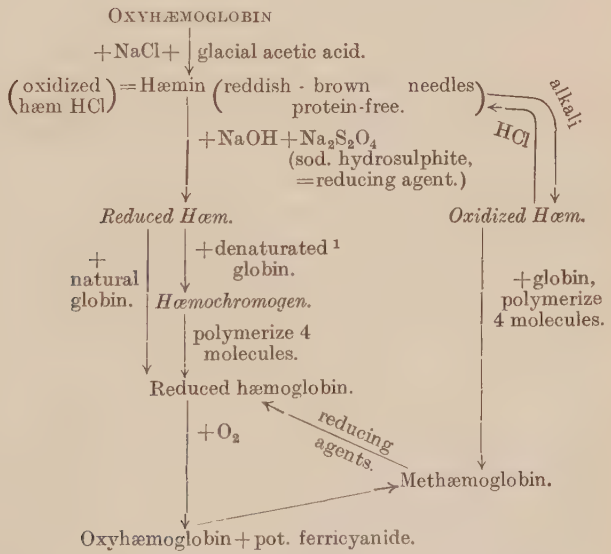
Blood Grouping (see p. 183).

Relation of Diet to Red Cell Formation. — Whipple examined the value of different diets for the formation of red cells and of hæmoglobin. Dogs are bled till the hæmoglobin is reduced to 50 per cent.: on a basal diet consisting of bread flour, starch, bran, sugar, salts, and vitamins the hæmoglobin remains at this low level. As hæmoglobin is continually undergoing destruction in the body, it is clear that on such a diet only enough hæmoglobin is being made to compensate for the daily loss ("replacement factor"), but it is not possible to restore the blood to its normal state. If a more favourable diet is given the hæmoglobin content tends to rise, but the anæmia is deliberately maintained at its previous level by repeated small bleedings; the total amount of hæmoglobin thus removed is a measure of the extra hæmoglobin formed under the influence of the new diet over and above the replacement factor. A quantitative idea is thus obtained of the effects

produced by the change of diet. Feeding with ox *liver* is associated with a maximal regeneration of red cells and of hæmoglobin; thus in a dog with a normal total hæmoglobin of 100 grm., there may be formed, in two weeks, under the influence of liver feeding, about 100 grms. of hæmoglobin over and above the replacement factor. *Heart* and skeletal *muscle* were found to be less useful. Green *vegetables* (which are rich in chlorophyll, which is closely related chemically to hæmoglobin) are not very effective. *Iron* was only found helpful in long continued severe hæmorrhage where iron shortage may have been present; *arsenic* and cacodylates are practically inert. Whipple believes that the liver contains stores of a "parent pigment substance"—a complex pigment which is utilized for the formation of hæmoglobin in the body. Whipple suggested that the control of anæmia in man by dietetic means should be investigated; the first result of this inquiry was the discovery of the curative action of liver extracts in pernicious anæmia (p. 205).

Hæmoglobin is a chromoprotein consisting of *globin* (a histone) united with a *pigment complex* consisting of *iron* in association with substituted *pyrrol* groups to which the name *hæm* has recently been applied. The following charts illustrate the relation of hæmoglobin to its more important derivatives.

CHART I

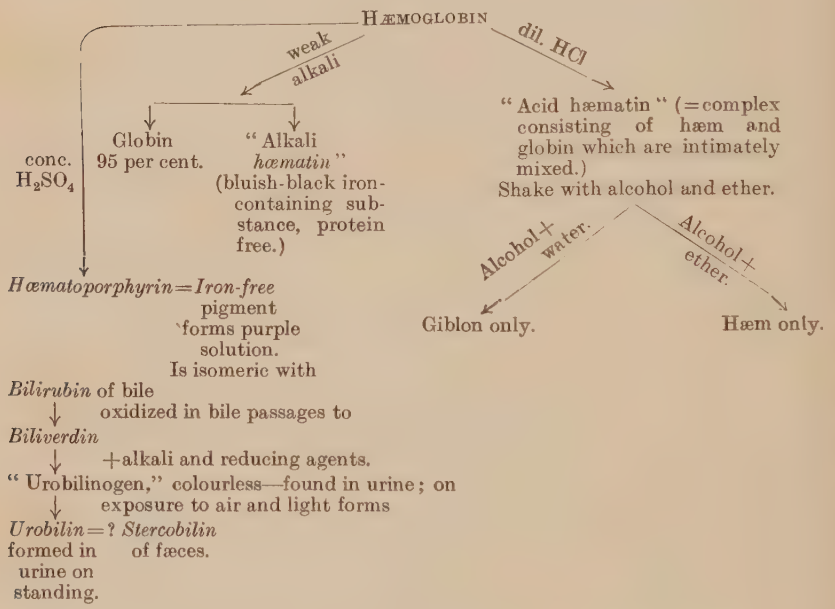


Reduced hæm is a base which is insoluble in water and in acid solutions, but is soluble in alkaline solutions; on oxidation it gives rise to oxidized hæm. Oxidized hæm and globin at *p*H 5 to 9 unite together and then four molecules become polymerized to form *methæmoglobin*; this is a dark brown

[1] A *denaturated* protein is one which has been artificially treated and which differs from the natural protein in certain respects.

substance which can be formed from oxyhæmoglobin by the addition of potassium ferricyanide (p. 331) or nitrites (p. 341). On treating methæmoglobin with reducing agents it is converted into reduced hæmoglobin. Methæmoglobin is thought to contain half the amount of oxygen present in oxyhæmoglobin, *i.e.* HbO compared with HbO_2; as indicated in the diagram the oxygen is probably in a different position in the molecule, and it is found that methæmoglobin does not give up its oxygen in a vacuum. Reduced hæm unites with denaturated globin to form *hæmochromogen*, four molecules of which polymerize to give reduced hæmoglobin; with natural globin reduced hæm unites to form reduced hæmoglobin directly; this readily becomes oxidized to oxyhæmoglobin.

CHART II


HÆMOGLOBIN
weak alkali
dil. HCl
Globin 95 per cent.
"Alkali hæmatin" (bluish-black iron-containing substance, protein free.)
conc. H_2SO_4
"Acid hæmatin" (=complex consisting of hæm and globin which are intimately mixed.)
Shake with alcohol and ether.
Alcohol + water.
Alcohol + ether.
Giblon only.
Hæm only.
Hæmatoporphyrin=*Iron-free* pigment forms purple solution. Is isomeric with
Bilirubin of bile
oxidized in bile passages to
Biliverdin
+alkali and reducing agents.
"Urobilinogen," colourless—found in urine; on exposure to air and light forms
Urobilin=? *Stercobilin* of fæces.
formed in urine on standing.

Hæmatoidin, found in old clots, is a mixture of iron-free pigments.

Hæmoglobin forms stable compounds with nitric oxide and carbon monoxide, *i.e.* NOHb and COHb respectively, which prevent further union with oxygen.

Before we can deal satisfactorily with the problem of the disposal of the red corpuscles, we must deal briefly with certain points in the structure of the spleen and the liver.

Structure of the Spleen.—The spleen is covered by a capsule which contains fibrous tissue and unstriped muscle. These plain muscle fibres contract at regular intervals (several times per minute), producing rhythmic variations in the volume of the spleen. It is possible that in this manner blood is squeezed out of the spleen and returned to the liver.

The arteries pass in at the hilum surrounded by connective tissue, and soon divide repeatedly. The smaller branches become surrounded by a mantle of lymphoid tissue which swells out in places to constitute the *Malpighian corpuscles*. These are ordinary nodules of lymphoid tissue which frequently present in their centre a group of large pale staining cells with indefinite outlines. The nature of these cells is not clear. In sections of spleen, the Malpighian corpuscles are scattered fairly uniformly through the substance of the organ, and show up clearly against the splenic pulp. They usually have a vessel in close relation to them.

The *splenic pulp* consists primarily of a reticulum or network of fibres derived from the fibrous trabeculæ passing in from the capsule and accompanying the incoming arteries. The most striking feature of the pulp is the great number of red cells found in its interstices. Some doubt exists as to the exact mode of termination of the splenic arterioles. They may end blindly and discharge their contained blood into the pulp, or they may be continued on into the venules. The practical difference is very slight, for the venules have *incomplete* walls which readily permit the passage of red cells in and out. There is no doubt, then, that the blood in the spleen comes into the most intimate contact with the cellular elements of the pulp.

The splenic venules are not lined by the usual flattened endothelium, but by large spindle-shaped cells, pointed at the ends and thick in the centre where a large prominent nucleus is present. These cells are loosely arranged leaving spaces between them, while surrounding them externally is a delicate basketwork of elastic fibrils.

The cells found in the pulp are of various kinds :

1. Elements of the blood : chiefly red cells and many lymphocytes ; the leucocytes present are few in number.

2. Special cells of the pulp—

(*a*) Large mononuclear cells, which are amœboid and phagocytic, and often contain red blood corpuscles in their substance in various stages of disintegration. They are often called "splenic" or "pulp" cells, or "*endothelial*" cells.

(*b*) Branched reticulum cells, which may possibly be of the same nature as the endothelial cells lining the venules.

(*c*) Giant cells, which are numerous in young animals and often contain ingested red cells.

Structure of the Liver.—It is well known that the portal vein, hepatic artery, and bile duct enter the liver surrounded by a connective tissue capsule and branch repeatedly in the substance of the organ. The branches of the portal vein surround the lobules as the *interlobular* veins, and from these vessels and their accompanying arteries blood passes between the columns of liver cells to reach the centre of the lobule to drain into the intralobular branch of the hepatic vein. It is known that the blood spaces in the interior of the lobule are incompletely lined with endothelium so that the blood is in contact in places with the liver cells. Similarly, the bile channels in the lobules are lined by the liver cells too. The difficulty hitherto has been to form a mental picture of the relationship between the liver cells, the vascular capillaries, the bile channels, and the lymphatics. M'Nee's well-known diagram (see Fig. 60) helps to simplify the matter. The liver is regarded as consisting not of solid columns of cells, but of a series of elongated tubules

or test-tubes with their closed ends against the central vein and the lumen passing into a branch of the bile duct. The interior of the tubes contains the bile, while the spaces between the tubes form the vascular capillaries. Incidentally, we may regard the unit of liver tissue as the group of tubules draining into one branch of the bile duct. The hepatic cells are granular, and polygonal in shape with indistinct outlines. Bile is formed in tiny vacuoles in the interior of these cells and is discharged through fine canaliculi into the bile capillaries. At the periphery of the lobule the hepatic cells become continuous with and transformed into the cubical cells lining the bile ducts. The blood between the tubules is also in direct contact with the hepatic cells. This is an ideal arrangement, as the liver has to transform

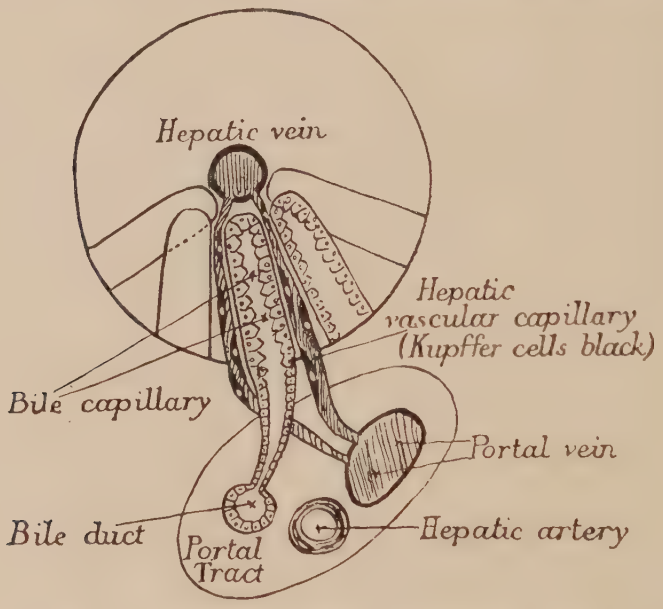


FIG. 60.—Diagram of Structure of Liver Lobule.—McNEE.

or modify many of the constituents of the blood. At intervals along the blood spaces are the *stellate cells of Kupffer*, which represent the remains of the original endothelial lining. They vary in number in different species. In man they are few, but in birds they are very numerous.

The Reticulo-Endothelial System.—This term was introduced by Aschoff to refer to cells which are scattered throughout the body but which, for all that, possess highly specialized functions. They have been separated from many cells of similar appearance by the method of intra-vitam injection of dyes. If carmine, for example, is injected intravenously into living animals, certain cells are found to retain the dye—*i.e.* the special cells of the splenic pulp, which we noted were called the "endothelial" cells of the spleen, certain branched cells in the bone marrow, the Kupffer cells of the liver, reticulum cells in lymph glands, and the interstitial cells of the testis.

Other endothelial cells, such as the ordinary lining of blood vessels, remain unstained. The relative importance of the different components of the system varies in different species, but in mammals the cells of the spleen and bone marrow play the chief rôle. The reticulo-endothelial system is concerned with blood destruction, and carries the disintegration of hæmoglobin as far as *bilirubin*. It is interesting to find the interstitial cells of the testis are included in this system, for there are many authorities who on other grounds deny that they possess any internal secretory activity and merely minister to the nutritional needs of the seminiferous tubules (cf. p. 166).

Fate of the Red Blood Corpuscles.—There is no doubt that the red blood corpuscles are continually undergoing destruction, because bilirubin—which is isomeric with the iron-free pigment, hæmatoporphyrin, formed outside the body from hæmoglobin—is constantly excreted in the bile. The red cells, after a few weeks of active life,[1] gradually become effete and are ingested by the phagocytic cells of the reticulo-endothelial system ; the lipoid envelope of the corpuscle is dissolved off and the hæmoglobin is liberated. Some red cells may first be broken down into small fragments, and hæmolysis of the corpuscles may perhaps occur in the blood stream itself.

Origin of Bilirubin.[2]—(1) *Histological Evidence.*—In the normal animal and particularly when blood destruction is actively proceeding, the cells constituting the reticulo-endothelial system, especially the phagocytic cells of the spleen and bone marrow (in mammals) are found to contain red cells in various stages of disintegration. Free hæmoglobin may be present in the cells and also iron in an inorganic form which gives the Prussian blue reaction. In birds after the injection of arseniuretted hydrogen, which is a powerful hæmolytic poison, the Kupffer cells of the liver are found to be full of débris of red blood corpuscles, and pigment—both iron-containing and iron-free—accumulates within them. They are stained with what appears histologically to be bile pigment. The Kupffer cells are shed and disintegrate, and possibly in this way bile pigment appears in the circulating blood.

(2) *Chemical* evidence is available that the formation of bilirubin is a widely distributed function. There is a trace of bilirubin in the circulating blood ; and the blood leaving the *spleen*, the *bone marrow*, and to a less extent the liver, contains definitely higher concentrations of bilirubin than the arterial blood, proving that bilirubin is formed in these organs.

[1] The average life of a red cell is believed by some authorities to be four to six weeks.

[2] The old view was that hæmoglobin, or some iron-containing derivative like hæmatin, was formed in the spleen and sent to the liver, where it underwent complete breakdown in the hepatic cells. The iron was removed and bilirubin was liberated and excreted into the bile. It was further argued that no other organ or tissue in the body, apart from the hepatic cells, could make bilirubin. This view is no longer tenable. The injection of arseniuretted hydrogen (AsH_3) in the goose produces great destruction of red cells, liberation of much hæmoglobin, and jaundice, *i.e.* staining of the tissues with the bile pigments which are formed in large amounts. After removal of the liver, the hæmoglobin is not broken down but is excreted unchanged in the urine (Minkowski). This was thought to prove that the liver was essential for bilirubin formation. In the goose, however, the spleen is very small and the Kupffer cells of the liver are very numerous. Extirpation of the liver is equivalent, therefore, to removal of the hepatic cells and of most of the reticulo-endothelial system too. One would expect bilirubin formation to be greatly diminished, seeing that its principal site of formation has been removed. The methods available at the time were incapable of demonstrating any small amounts of bilirubin which might still have been formed.

(3) There is no doubt whatever, that the liver is *not* essential for bilirubin formation. After total extirpation of the liver, bilirubin rapidly accumulates in the body—the plasma and body fat are coloured yellow and definite jaundice is present in animals which survive more than six hours (cf. p. 399). Jaundice develops almost as rapidly if the spleen is removed as well, proving that the phagocytic cells of the bone marrow are important sites of bilirubin formation.

(4) After splenectomy (in the intact animal), compensatory hypertrophy of the rest of the endothelial system takes place, and the rate of bilirubin formation is not appreciably diminished.

Two types of bilirubin can be distinguished by means of *van den Bergh's* sensitive reaction. :

1. Bilirubin found as a result of the breakdown of hæmoglobin in serous cavities, or during rapid hæmolysis in the blood stream.

2. Bilirubin, which has passed through the liver cells into the bile or else has been shunted back into the blood stream because of obstruction to the bile passages.

The reagents used in van den Bergh's reaction are as follows :

A. Sulphanilic acid, 1 c.cm. ; conc. HCl, 15 c.cm. ; distilled water, 1000 c.cm.

B. Sodium nitrite, 0·5 grm. ; distilled water, 100 c.cm.

Mix 25 c.cm. A. and 0·75 c.cm. B. immediately before use. Allow the blood which is to be tested to clot, and use the serum.

Two reactions are described :

i. *Direct reaction* : Mix 1 c.cm. of serum and reagent. A bluish violet colour develops and reaches its maximum in 10 to 30 seconds.

ii. *Indirect reaction* : Add 2 c.cm. 96 per cent. alcohol to 1 c.cm. serum ; centrifuge and pipette off 1 c.cm. supernatant fluid. Add to it 0·5 c.cm. alcohol and 0·25 c.cm. of reagent. A violet red colour develops and is maximum instantly.

The bilirubin poured into the blood stream by the reticulo-endothelial system gives the *indirect* reaction only, *i.e.* it needs the addition of alcohol to give the colour change. But during its passage through the liver cells into the bile capillaries it is modified in some way, so that now the addition of alcohol is not necessary—the *direct* reaction is obtained. To be decisive, the colour change must come on in 10 to 30 seconds (*prompt* direct reaction). A *delayed* direct reaction (appearing in 1 to 15 minutes) has the same significance as an indirect reaction.

Biliverdin is only formed in the bile passages as a result of the oxidation of bilirubin : it is not present in the blood stream. It does not give the van den Bergh reaction.

Application to Jaundice.—In the past all types of jaundice were regarded as *hepatogenous* in origin, and all were explained as resulting from some form of obstruction in the bile capillaries which caused the bile pigments to pass back into the blood stream. In many cases, however, no obstruction could be demonstrated. Our new knowledge makes the classification of the forms of jaundice much easier.

Theoretically, jaundice may arise as follows (McNee) :

1. Obstructive Jaundice.—(*a*) The bile pigment is formed normally in the reticulo-endothelial system and is secreted by the liver cells into

the bile capillaries. Owing to some obstruction the bile is dammed up and passes into the systemic circulation *via* the lymphatics or directly into the hepatic vascular capillaries. The jaundice due to stone in the common bile duct, or other gross cause for obstruction such as carcinoma of the head of the pancreas, is readily understood. The bilirubin thus reabsorbed into the blood has previously passed through the liver cells and so gives a (prompt) direct van den Bergh reaction.

(*b*) There is probably an obstructive factor in certain other forms of jaundice. In inflammatory conditions of the liver and bile ducts, the bile capillaries become plugged with an albuminous coagulable substance. This is followed by rupture of the distended bile capillaries and the passage of bile into the blood (Eppinger).

(*c*) In jaundice due to hæmolytic agents the bilirubin content of the bile is considerably raised. The bile is so viscid as practically to block the ducts, and actual bile thrombi may be detected. Here, too, some bilirubin may pass back into the circulation.

(*d*) In some virulent infections of the liver, such as acute yellow atrophy, widespread necrosis of liver cells occurs. Possibly many liver columns are completely cut off from their bile capillaries, and any bile which they may still form passes back into the blood.

2. Toxic and Infective Jaundice.—If the liver cells are poisoned, they become relatively incapable of secreting bilirubin from the blood into the bile capillaries. Bilirubin consequently accumulates in the blood and stains the tissues. The jaundice is due to excess of bilirubin in the blood which has *not* passed through the liver, and so the *indirect* van den Bergh reaction is obtained (or possibly a delayed direct reaction). The above type of jaundice occurs complicating the infectious fevers (*e.g.* pneumonia, typhoid); or following the action of the unknown poison of acute yellow atrophy; or from certain drugs like chloroform and salvarsan. Histologically, the liver shows any degree of change, from cloudy swelling or fatty change, to actual necrosis of few or many cells.

As suggested above, 1 (*b*), 1 (*d*), an obstructive element may also be present in these conditions, and so complicate the van den Bergh reaction. A *biphasic* reaction may be obtained: the bilirubin in the blood due to obstruction of the ducts gives a prompt direct reaction, while the bilirubin dammed up from poisoning of the liver gives a delayed direct reaction, *i.e.* a reddish colour first appears which after a varying interval deepens to a violet.

3. Hæmolytic Jaundice.—This results from excessive destruction of red corpuscles and the formation of bilirubin in larger amounts than the hepatic cells can deal with. The excess of bilirubin thus accumulates in the systemic circulation. Such hæmolytic agents as arseniuretted hydrogen, toluidine-diamine produce this type of jaundice.

The lemon yellow tint of Pernicious Anæmia is really due to a low grade of jaundice.

In Acholuric Jaundice, as already noted, the red corpuscles are abnormally fragile and so tend to be destroyed excessively with resulting slight hæmolytic jaundice. The French authorities (Widal, Chauffard) demonstrated that in these types of jaundice bilirubin accumulates in the blood, but that the bile acids pass out normally into the intestine and their concentration in the blood does not rise. Hæmolytic jaundice is therefore a " pure pigmentary

cholæmia " or " *dissociated jaundice* "—the bile salts being treated differently from the pigments.

Although we have divided jaundice into three great groups, it is obvious there will be considerable overlapping. Poisoning of the liver cells is often associated with inflammation of the bile ducts, and so with an obstructive element; similarly in hæmolytic jaundice the increased viscosity of the bile may result in blockage of the bile capillaries; and even in gross obstructive jaundice the functional activity of the liver cells will be depressed. Both forms of bilirubin will therefore be present in the blood, and the biphasic type of reaction may occur frequently.

Biliuria.—In obstructive jaundice bile pigment appears in the urine when the concentration of pigment in the blood exceeds $\frac{1}{50000}$. In hæmolytic jaundice the concentration of bilirubin may reach $\frac{1}{12000}$ without any pigment escaping in the urine. The renal threshold, then, is different in the two types of jaundice, and no satisfactory explanation of this discrepancy is available.

Fate of the Bile-Pigments.—In the large intestine the bile pigments are reduced by putrefactive organisms into a pigment which is partly excreted with the fæces (*stercobilin*) and partly reabsorbed into the portal circulation (" urobilin," which is probably identical with stercobilin). It is believed that most of the urobilin passes back to the liver where it may be stored and perhaps be used in the formation of fresh hæmoglobin.

Some of the pigment escapes in the urine in the form of *urobilinogen*, a colourless compound, which on exposure to air and light forms urobilin once more. In *insufficiency of the liver*, urobilin enters the systemic circulation in larger amounts and may be readily demonstrated in the urine.

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McNee.—*Quart. Journ. Med.*, 1922–23, vol. xvi. p. 390 (Jaundice).
Maximow.—*Physiol. Rev.*, 1924, vol. iv. p. 533.
Rich.—*Ibid.*, 1925, vol. v. p. 182.
Rous.—*Ibid.*, 1923, vol. iii. p. 75.
Sabin.—*Ibid.*, 1922, vol. ii. p. 38; *ibid.*, 1928, vol. viii.

Pernicious Anæmia is a disease characterized by the following features: The red cells are greatly reduced in number, are abnormal in shape, and tend to be larger in size than usual[1]; the hæmoglobin of the blood is less reduced than the red cell count so that the colour index (p. 195) is high and often exceeds 1·; young red cells (reticulocytes) and nucleated red cells may be seen. The white cells (especially the leucocytes) and the platelets are also reduced in number. Post mortem the red marrow is found to be intensely hypertrophied and to extend into and finally completely fill the shafts of the long bones. The disease pursues a fluctuating course with alternating periods of *remission* when the blood picture is fairly normal and the clinical condition is good, and of *relapse* when the anæmia is severe and the patient is gravely ill. The cause of the anæmia is not yet known. Complete *achlorhydria* is present in all cases, and it is suggested that the absence of HCl from the stomach permits virulent organisms, *e.g.* streptococci, to pass into the small intestine where they settle and elaborate toxins. The toxins may

[1] Some cells which are smaller than normal (diameter $=4\mu$) are also present (p. 195).

damage the central nervous system, and destroy the medullary sheaths of the fibres in various columns of the cord, producing a condition known as *subacute combined degeneration*. Some workers believe that the toxin can also act as a hæmolytic agent which causes excessive destruction of red cells ; in support of this view is the raised bilirubin content of the serum (which produces a low grade of jaundice), and the intense phagocytosis of red cells in the spleen, lymph glands, and bone marrow.

The other view is that in pernicious anæmia the bone marrow is primarily at fault. Peabody[1] has examined portions of the marrow of the middle of the tibia which were excised during life in periods of relapse and of remission. During the relapse the marrow is extremely cellular and contains little fat ; the erythropoietic capillaries (p. 193) are filled with enormous numbers of megaloblasts in active mitosis ; normoblasts are scanty. During the remission a more normal picture is presented by the marrow : it is fatty and contains few cellular elements. The erythropoietic capillaries contain normoblasts and erythrocytes. Peabody suggests that during the relapse, although the marrow shows signs of intense activity it is functioning inefficiently ; many megaloblasts are formed, but they *do not mature* into red cells and so few erythrocytes are supplied to the circulating blood ; the megaloblasts themselves are not swept into the circulation in any numbers owing to their adhering one to the other.

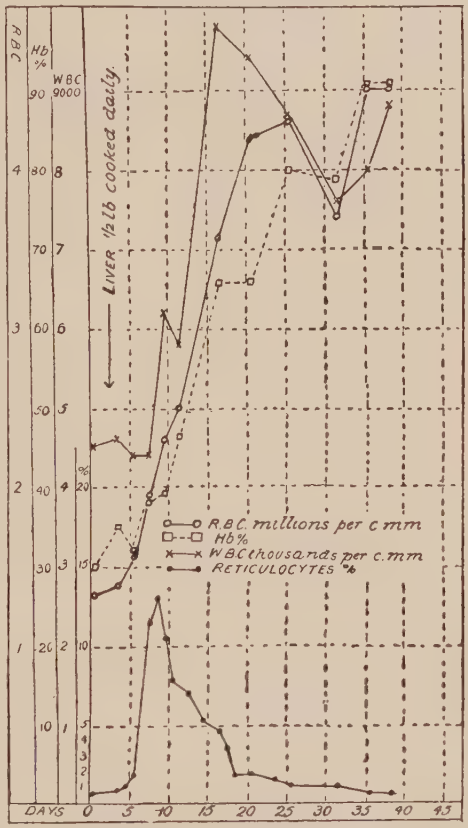


Fig. 61.—Liver Treatment of Pernicious Anæmia. (Brewer, Wells, and Fraser, *Brit. Med. Journ.*, 1928, vol. i.)

Minot and Murphy [2] have shown that feeding with diets rich in liver has a remarkable curative effect in pernicious anæmia. Cohn [3] has prepared a liver extract free from iron, protein, and the known vitamins, which is equally efficacious. Within a few days of commencing treatment the reticulocytes

[1] Peabody, *Amer. Journ. Pathol.*, 1927, vol. iii., p. 179.

[2] Minot and Murphy, *Journ. Amer. Med. Assoc.*, 1926, vol. lxxxvii. p. 470 ; *ibid.* 1927, vol. lxxxix. p. 759.

[3] Cohn *et al.*, *Journ. Biol. Chem.*, 1927, vol. lxxix. p. 69.

in the blood increase in number, may reach 15 to 40 per cent. of the total red cells and then decline (see Fig. 61).

The red cell count and total hæmoglobin begin to increase a little later; the improvement continues after the reticulocyte count has begun to decline and persists until a normal blood picture is established. The colour index falls below unity, the excessively large erythrocytes disappear and the bilirubin content of the blood returns to normal; the achlorhydria, however, is unaffected. There is a striking improvement in general clinical condition. The mode of action of liver extract is unknown; it may stimulate the marrow to provide mature red cells or it may provide a constituent which is essential for the maturation of normal red cells. Contrary to expectations, liver treatment has been found less useful (in man) in cases of secondary anæmia, such as that resulting from hæmorrhage (cf. p. 196).

White Blood Corpuscles.—We may classify the white blood corpuscle into three groups.

1. *Granulocytes* characterized by the presence of granules in the cell protoplasm and a nucleus which consists of 3 to 5 lobes. The term "leucocyte" is often applied particularly to this type of cell, though it is also used less precisely to include all varieties of white corpuscles. Using Jenner's stain three types of cells are recognized by the character of their granules: neutrophil, esoinophil, and basophil (Fig. 57).

2. *Lymphocytes*: these are round non-granular cells with large round nuclei which practically fill the cell substance. They are divided into large and small lymphocytes (Fig. 57).

3. *Monocytes*: this is a convenient term used to describe a group of cells which are very ill understood, but suffer from a multitude of labels. The group includes the mononuclear cells, hyaline and transitional cells among others. They are large pale cells with a pale-staining round or indented nucleus and non-granular protoplasm.

The average number of white corpuscles is 6000 to 8000 per c.mm., made up as follows: leucocytes 70 per cent. (neutrophil 65, eosinophil 5, basophil 0·5), lymphocytes 25 per cent., monocytes 5 per cent.

Development of White Corpuscles.—As previously stated (p. 189), the white corpuscles develop in the mesoderm of the embryo and migrate secondarily into the blood vessels. In extra-uterine life the granulocytes develop normally exclusively in the red marrow; the lymphocytes and monocytes also develop to a slight extent in the marrow but their main site of origin is in the lymphoid tissues of the body.

Granulopoiesis.[1]—The process can be well studied in the simplified marrow of pigeon or rabbit as described above (p. 191). Myeloid activity is best seen at the periphery of the marrow in close proximity to *dilated* sinuses, and is wholly an *extra-vascular* process (Figs. 62 and 63). Between the fat cells, branched *reticulum* cells can be seen irregular in outline, free from granules or mitochondria, and with faintly basophil cytoplasm (Plate, Fig. 6). These cells multiply by mitosis to give rise to the *primitive white blood cell* (Plate, Figs. 7 and 8): the nucleus is large and round and surrounded by a thin rim of basophil protoplasm which contains large rod-shaped mitochondria. This cell enlarges to become the *myeloblast* (Plate, Fig. 9): the

[1] Doan, Cunningham, and Sabin, *Contribution to Embryology*, Carnegie Publications, 1925, vol. xvi. p. 227.

nucleus tends to be bean-shaped, the mitochondria are very numerous and tend to lie in the concavity of the nucleus. The next stage is the *myelocyte*, which is characterized by the appearance of *granules* in the cytoplasm (Plate, Figs. 10, 11, and 12). Sabin recognizes three stages in the development of the myelocyte—Types A, B, C, according to the number of granules which are present. Type A contains few granules and many mitochondria; Type C, many granules and few mitochondria; Type B is intermediate. Most of the myelocytes contain neutrophil granules, but some contain eosinphoil or basophil granules. Sabin has described a case of leukæmia in which many myeloblasts were present in the circulating blood. As a result of a blood transfusion the myeloblasts underwent maturation in the *circulating blood* into myelocytes.

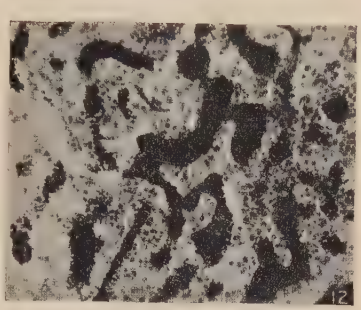


Fig. 62.—Marrow of Pigeon. Zone of granulopoiesis 24 hours after feeding following hypoplasia induced by starvation. Vessels injected with Indian ink. Practically every vessel in the field is widely dilated and well filled with ink. In the intervascular spaces are numerous *myelocytes*. Contrast with Fig. 56. (Doan, Cunningham, and Sabin.)

Each type of myelocyte gives rise to the corresponding *leucocyte*; the nucleus indents, and then becomes lobed; the granules, in fresh preparations, instead of being motionless, show dancing or streaming movements, and the cytoplasm becomes more liquid, so that amœboid movements occur. The more mature white cells are found lying just external to the sinusoids, and pass actively through the *intact* endothelial lining of these vessels into the circulation. *Senile* leucocytes lose their motility, the granules are still and no longer stain with neutral red, and the cells break up readily in films.

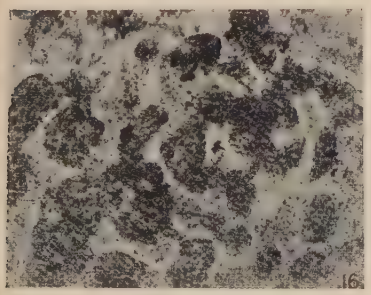


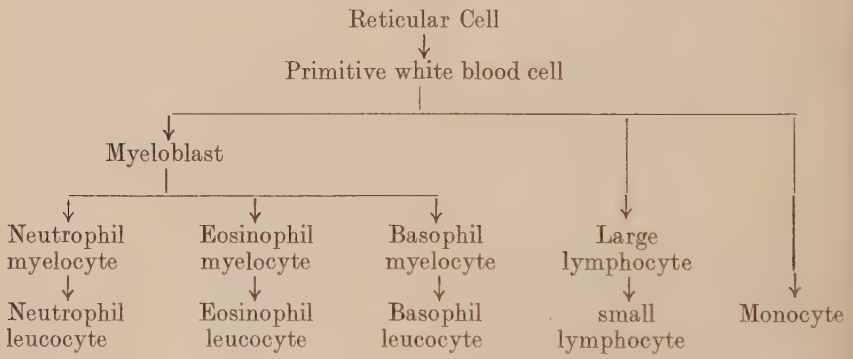
Fig. 63.—Uninjected Marrow of same Pigeon as shown in Fig. 62 showing engorged vessels. (Doan, Cunningham, and Sabin.)

According to Sabin, "showers" of senile cells can be seen two or three times a day in the circulating blood, when they may constitute 30 to 50 per cent. of the granulocytes. As the senile cells probably undergo rapid destruction, these findings suggest that the granulocytes function for only a few brief hours in the blood stream. This may be correlated with the fact that in normal *marrow* 75 per cent. of the cells are myeloid and only 25 per cent. are erythroid, although the ratio of white to red cells in the *blood* is about 1 : 1000. The myeloid cells found in marrow are (per 100 cells counted) neutrophil myelocytes; Type C 86, type B 4, type A 0·4, eosinophil myelocytes 2·5, basophil myelocytes 1·2, myeloclasts 1·1, polymorphs 5. It will be noticed that the predominant cell is the Type C myelocyte, *i.e.* the immediate precursor of the leucocyte (cf. p. 193).

Under certain circumstances, the primitive white cells which are found in the spleen, instead of giving rise to lymphocytes or monocytes, may give rise to the myelocyte series of cells.

Development of Lymphocytes.—These are normally the least conspicuous elements in the marrow, although definite clumps of large and small lymphocytes can be found round the blood vessels. The small lymphocyte is probably derived from division of the large lymphocyte, which is derived, according to Sabin, from the primitive white cell of the marrow. In conditions associated with lymphocytosis, and in lymphatic leukæmia, the lymphocytes become very numerous in the marrow and overshadow the other types of cells. Probably, in health, lymphocytes are chiefly formed in the lymphoid tissues of the body such as the lymph glands, spleen, thymus, tonsils, and Peyer's patches [aggregated lymphatic nodules].

Monocytes.—These probably constitute a separate line of development from the primitive white cell in the marrow and in lymphoid tissues. The myeloblasts can be distinguished from the monocytes, which they closely resemble, by the *indophenol reaction*. All the granulocytes and their non-granular precursors contain an oxidizing ferment which produces an intensely blue colour (indophenol blue) with α-phenol and dimethylparaphenyldiamine ; this reaction is not given by the monocytes. The development of the white corpuscles may be thus summarized.



Functions of White Blood Corpuscles.—The polymorphs produce a trypsin-like ferment which acts best in an alkaline or neutral medium and effects the digestion of proteins (Opie). Its action, however, is normally combated by an " anti-enzyme " which is present in the plasma and the tissue fluids generally. According to Jobling and Petersen, this anti-enzyme is a soap or some other combination of an unsaturated fatty acid, which is inactivated by heat (over 70° C.) and by saturating the fatty acid with iodine.

The polymorphs ingest foreign particles and dissolve them by means of their proteolytic enzyme. If this enzyme (" leucoprotease ") diffuses out into the plasma, it is destroyed by the anti-enzyme which is present there in excess. In areas of inflammation the polymorphs are present in large numbers, and large amounts of enzyme pass out from the disintegrated leucocytes. The anti-enzyme is outstripped and liquefaction of the dead tissue occurs, with the formation of an abscess.

The lymphocytes and mononuclear cells produce a proteolytic ferment which resembles pepsin and acts only in a feebly acid medium ("lympho-protease").

Inflammation.—The vascular phenomena of inflammation appear to be due to the stimulus of substances liberated from the dead or injured tissues.[1] Great dilatation of the arterioles and capillaries occurs, probably because the toxins thus formed directly paralyse their muscular walls. Many capillaries, which were previously closed, lose their tone and open up to receive blood. At first, because of the arteriolar dilatation, the blood courses rapidly from the arteries to the veins. We shall see (p. 306) that whenever the capillaries are dilated their permeability increases. Clear fluid exudes from the blood into the surrounding tissue spaces, bringing the various antibodies of the blood to the threatened region. The part is swollen from this accumulation of fluid (inflammatory œdema) and hot because of the increased amount of blood received. As more fluid is lost from the capillaries, the red corpuscles tend to form clumps and consequently the blood stream is increasingly slowed. Possibly the endothelial lining of the capillary gets "stickier" and thus interferes with the rate of flow. The corpuscles at first tend to remain in the centre of the capillary as an "axial stream"; then the leucocytes become adherent to the roughened capillary lining and are thus prevented from being swept on. They soon force a way out through the capillary wall and escape into the crevices of the tissues, where they wander about. It is believed that a diffusible chemical substance is liberated from the dead or tissue cells which attracts the leucocytes. The poisons of the invading bacteria appear to possess a similar "*chemiotactic*" influence. The bacteria are dealt with by the leucocytes and the antibodies which have exuded from the plasma. The débris is liquefied and removed by leucocytes and other cells.

The chemical substances which attract the white corpuscles locally also pass into the blood stream and stimulate overgrowth in the red bone marrow. It is found that, depending on the nature of the infection, different types of cells are attracted to the damaged region, and proliferation of different cells occurs in the bone marrow.

Neutrophil Leucocytosis occurs in many inflammatory processes, for example, in pneumonia, endocarditis, and septic infections. The neutrophils may number 20,000 to 40,000 or even 150,000 per c.mm., and constitute 90 to 95 per cent. of the total white count. Great multiplication of the myelocytes occurs in the marrow, and leucocytes are discharged into the blood stream in enormous numbers.

A leucocytosis which is slight and variable in degree is said to occur at the height of digestion. According to B. Shaw, during physiological rest, the number of leucocytes in the peripheral blood is subject to considerable and rapid fluctuations, though there are phases when a state of equilibrium exists. There is no evidence that the ingestion of milk, casein, water, or fat influences the leucocyte content of the peripheral capillary blood.

Lymphocytosis occurs in typhoid fever and in the more chronic inflammatory conditions. Lymphocytes predominate in the tissue response to the tubercle bacillus, and are found surrounding, and attempting to check the spread of, new growths. In lymphocytosis, hyperplasia of the

[1] It is not known whether a histamine-like substance is responsible for the vascular changes in inflammation (cf. p. 295, *et seq.*).

marrow occurs, and lymphocytes form the predominant element found there histologically.

Eosinophilia, an excess of eosinophil leucocytes in the circulating blood, occurs in infections with parasitic worms, like *Ankylostoma duodenale* or *Trichina spiralis*; in asthma; in scarlet fever, and many diseases of the skin. The marrow shows great proliferation of the eosinophil myelocytes.

Blood Platelets.—*Origin.*—The platelets develop from the giant cells (*megalokaryocytes*) of the red marrow; these are cells which may attain a diameter of 40μ and contain an irregular lobed ring of nuclei. Their appearance suggests that they arise from the growth of a marrow cell, and multiplication of its nuclei without the formation of dividing cell membranes. The giant cell is amœboid and finds its way into the circulation whenever the white blood count is high. Normally it throws out pseudopodia which pass through the wall of the sinusoids and constrict off part of their substance to form the blood platelets. With Leishman's stain, the platelets appear as round or oval bodies with faint blue protoplasm and distinct reddish-purple granules. If the stain is precipitated on the granules an appearance simulating a nucleus is produced. The platelets number 250,000–400,000 per c.mm.; each is about one-third the size of a red blood corpuscle. The total number varies with the number of giant cells in the red marrow. They are thus increased in myeloid leukæmia and in Hodgkin's disease (where they may exceed one million per c.mm.), and are diminished in pernicious anæmia (in which disease the giant cells in the marrow are scanty) and after large doses of X-rays, which destroy the marrow. In severe infections of the marrow the platelets may completely disappear. The platelets are possibly destroyed in the *spleen*, because after splenectomy their number increases, although only temporarily.

Functions.—(i) When blood is shed the platelets disintegrate and liberate a phospholipine (cephaline) which initiates the process of coagulation (p. 186). If a film of clotting blood is examined it is noted that filaments of fibrin radiate from the vicinity of altered platelets. As previously pointed out, the number of the platelets is unaltered in hæmophilia, although the coagulation is greatly prolonged in this condition (p. 188).

(ii) The platelets protect injured or abnormally permeable epithelia of blood vessels (pp. 187, 211). If the capillary defect leads to loss of blood the circulating platelets are affected (α) by loss of platelets equivalent to the amount of blood escaping, and (β) by adhesion of platelets to the threatened zone.

(iii) The platelet count is diminished in vitamin A deficiency, in which condition they may serve as agglutinins to clump the invading organisms (p. 444).

(iv) There is considerable evidence that diminution in the number of the platelets (*thrombopenia*) is associated with *purpura*. The term purpura is used to designate a condition in which there is a tendency to spontaneous hæmorrhages beneath the skin, from the various mucous membranes and in some cases into the internal organs (Holt). Purpura may be *symptomatic* or *primary*. Symptomatic purpura may result from various infections (*e.g.* infective endocarditis, typhus) from toxins and in cachectic states (*e.g.* cancer). Primary purpura occurs most often in children and has no constant associations with other maladies. The characteristic features of purpura, apart from the spontaneous hæmorrhages, are:

(a) The *coagulation time* of shed blood is unaffected (*i.e.* 5 to 10 minutes),

but the clot does not retract to form a firm mass of fibrin. (β) The *bleeding time* is definitely prolonged : if the ear is pricked and the blood dried off with blotting-paper every ¼ or ½ minute, bleeding normally ceases after 2 to 4 minutes ; in purpura, bleeding may persist for 10, 20 minutes, or even longer. (γ) The *resistance* of the capillaries is diminished : if a tourniquet is firmly bound round the arm for 2 minutes, a crop of minute hæmorrhages under the skin (petechiæ) appears. (δ) The number of platelets bears a close relationship to the severity of the hæmorrhages. In mild cases of purpura (*P. simplex*) the count is slightly lowered, but in severe cases of the disease (*P. hæmorrhagica*) with prolonged and extensive bleeding the platelets may be completely absent. According to Duke, when the number of platelets is below 60,000 there is an abnormal tendency to bleed, below 10,000 hæmorrhages are severe, below 1000 fulminant. It cannot be argued, however, from these results, that the thrombopenia is responsible for the occurrence of hæmorrhages because the bleeding may cease in a severe case several days before the platelet count rises, and the platelets have been known to disappear from the blood without hæmorrhages occurring. The experimental work of Bedson has thrown some light on the subject. The injection of agar serum into an animal reduces the platelets to a low figure but does not produce hæmorrhages. If, however, an injection of an anti-red-cell serum is made four hours previously, the injection of the agar serum rapidly produces purpura. Bedson suggests that the anti-red-cell serum injures the capillary endothelium which is closely related genetically to the erythrocytes. Normally the platelets would be deposited on the injured areas and act as protective agents ; but if the platelets are previously destroyed (by agar serum) the damaged capillary endothelium is left unprotected and hæmorrhage results. *Abnormal capillary permeability* to blood may then be the initial disorder in purpura ; the *platelets are reduced in number secondarily*, as they are used up to defend the weak areas. If the capillary damage is slight, the platelet count falls, but the defensive work has been satisfactorily carried out ; if the endothelial damage is widespread, all the platelets may be used up without supplying adequate protection, and severe hæmorrhage occurs. In this way the platelet count will be lowered proportional to the degree of capillary damage, and therefore to the tendency to bleed.

Splenectomy has been carried out in a number of cases of severe purpura on the hypothesis that the seat of the disease was in the spleen which was destroying platelets excessively ; although this hypothesis is probably incorrect (*v. supra*), yet in many instances following this operation there is an immediate cessation of the hæmorrhages and a rapid rise in the blood platelets. The increase in the number of platelets in the circulation may protect the damaged capillaries and arrest the hæmorrhages. Many points, however, are still obscure. Bedson found that splenectomy in the normal guinea-pig protects against the production of experimental purpura, but only so long as the increase in platelets is present. But the increase in the number of platelets after splenectomy is temporary, and yet the operation may cause prolonged arrest of the hæmorrhages clinically.

The Spleen.—The *structure* of the spleen was described on p. 198. The principal points in the histology of the organ are :

1. Nodules of lymphoid tissue (Malpighian corpuscles) [splenic lymphatic nodules] surrounding the smaller arterioles.

2. Venules lined by a modified endothelium which communicate freely by means of numerous crevices with the splenic pulp.

3. Certain reticulum and phagocytic cells in the pulp, which are important representatives of the reticulo-endothelial system in man.

4. Intimate contact between the blood and the cells of the pulp.

Extirpation of the spleen has been known, since the earliest times, not to be followed necessarily by any marked disturbance of health. As the spleen is obviously not essential to life, it has been customary in the past to minimize its importance. There is little doubt that it plays a very important rôle in the body, and its close relationship to the blood and vascular system has been clearly demonstrated.

Size of the Spleen.—The spleen is a very much bigger organ during life than would be suspected from examining it after death. The variations in size which may occur in the living animal may be studied as follows :

(i) Open the abdomen in anæsthetized animals and attach small metal clips to the margins of the spleen ; the organ is X-rayed from different angles, and solid casts are constructed from a study of the photographs.

(ii) A portion of the abdominal wall is removed and replaced by a mica flap through which the spleen may be inspected.

(iii) The spleen may be withdrawn from the abdomen and fixed externally ; if aseptic precautions are taken and the blood supply of the spleen is not interfered with, it may function actively in this new position outside the body (" extra-abdominal " spleen).

In the living cat the spleen is found to be four times as large as the anatomical or post-mortem organ, and to constitute 1 per cent. of the weight of the animal.

Functions of the Spleen

1. Blood Formation.—(i) We have previously noticed that during the latter months of fœtal life the spleen is actively engaged in forming red blood corpuscles. In states of emergency, as in anæmia, this function may be resumed in post-natal life. (ii) The Malpighian corpuscles are merely nodules of lymphoid tissue, and by their proliferation may add to the number of lymphocytes in the circulating blood.

In the blood diseases called the leukæmias, the normal cells of the splenic pulp disappear, and are replaced by masses of lymphoid cells in lymphatic leukæmia, and by numerous myelocytes in the myeloid type of leukæmia.

2. Blood Destruction. We have seen that the spleen forms an important part of the reticulo-endothelial system, and so is actively concerned in blood destruction. The cells of the pulp ingest and break down red blood corpuscles, remove the iron from the hæmoglobin molecule, and elaborate bilirubin which is then discharged into the blood (p. 202). After extirpation of the spleen, these functions are carried out vicariously by other representatives of the reticulo-endothelial system, such as the Kupffer cells of the liver and the reticulum cells of the bone marrow and lymph glands. The *blood-platelets* are possibly destroyed in the spleen (pp. 211–216).

3. Reservoir of Red Corpuscles.—The recent observations of Barcroft and his co-workers have clearly shown that the spleen forms an important reservoir of red blood corpuscles, which are held there to meet circumstances

in which an increased amount of hæmoglobin is required in the circulation. It can be shown that the splenic pulp is a sort of backwater through which the blood circulates with extreme slowness. Thus if animals are given air containing small amounts of carbon monoxide to breathe, so that the hæmoglobin only becomes about 2 per cent. saturated with the gas, no CO whatever may penetrate into the splenic pulp. If larger amounts of gas are inhaled, the splenic pulp is found to lag about thirty minutes behind the general circulation in the extent of the saturation of its hæmoglobin with CO. Again, if the animal is put in the fresh air and allowed to get rid of its carbon monoxide, the splenic pulp lags about ninety minutes behind the general circulation. These experiments clearly show that under resting conditions the splenic pulp is practically cut off from the general blood stream. Although under experimental conditions small *rhythmic peristaltic contractions* of the spleen occur, they do not appear to help the interchange of blood between the pulp and the venules. On the other hand, they may compress the veins of the spleen and help in returning their contained blood to the liver.

It can be shown that oxygen-lack (anoxæmia), from any cause, causes the spleen to contract and diminish in volume. The red blood corpuscles contained in the splenic pulp are consequently discharged and made available for the general purposes of the body.

(i) In CO poisoning the spleen contracts, and thus unaffected red blood corpuscles are provided for oxygen-carrying purposes.

(ii) If successive *bleedings* are carried out, the spleen contracts on each occasion, and if the animal is bled to death, the final size of the organ is only one-quarter of that found originally. In an animal killed by bleeding to 60 c.cm. the spleen was found to diminish in size from 24 to 4·1 grm., thus supplying 20 grm. of substance to the blood. This material, from analysis of the blood of the splenic vein, proved to be rich in red blood corpuscles. If the splenic artery is clamped and the splanchnic nerves are stimulated, the blood is expelled from the splenic pulp into the veins and is found on analysis to contain about 115 per cent. of hæmoglobin. It would appear from this that about one-quarter of the total red cells in the body may be stored in the spleen and only become available in times of stress. This gives us an idea to what extent the spleen functions as a reservoir, or " parking ground," of red corpuscles.

(iii) In exercise, when there is a great demand for oxygen-carrying capacity, the spleen diminishes (in the cat) from 26 to 13 grm., supplying about 13 grm. of material rich in red cells to the blood.

(iv) On ascending a mountain-side one is exposed to a *rarefied atmosphere* and a rapid increase in the red corpuscle count takes place, which is too sudden to be accounted for by proliferation of the bone marrow and is probably due to contraction of the spleen.

(v) It was found during an expedition to Peru that when the tropical regions were reached where the external temperature was high, the blood volume as determined by the carbon monoxide method increased. There was an increase, too, in the total amount of hæmoglobin and here, too, the whole process appeared to be too rapid to be accounted for by proliferation of cells in the bone marrow. Probably what occurred was as follows: owing to the rise of external temperature, large vascular areas were opened up in the skin in order to facilitate the giving off of heat. The extra fluid required

to fill these vessels was called up from the tissue spaces in the deep organs, and to prevent the oxygen capacity of each unit of blood from diminishing, the stores of red cells in the spleen were called upon as well. As the external temperature fell and the skin areas underwent vaso-constriction, the reserve red cells were demobilized and returned to the splenic pulp. The blood volume thus appears to be a physiological variable adjusted to meet the requirements of the body. The spleen appears to regulate the number of red cells in use at any time. By means of its reticulum it can enmesh and retain many corpuscles; and in times of need it can expel them into the circulation.

The spleen contracts in virtue of the smooth muscle found in the capsule. Oxygen-lack appears to affect the central nervous system and result in stimuli being sent to the spleen along the splanchnic nerves. Contraction of the spleen does not take place when its nervous connections are severed. The composition of the blood bathing the spleen is of no importance. Thus the spleen contracts while it is perfused within the body with normal blood, if the animal as a whole is poisoned with carbon monoxide to produce oxygen-lack in the nervous system.

To illustrate the functional importance of the spleen, a series of animals were exposed to carbon monoxide. Some of the animals had been splenectomized, while the others had been previously subjected to an abdominal operation of similar severity. The splenectomized animals died on the average in about seventy minutes, while the controls survived for over twenty minutes longer. This demonstrates the value of the store of unpoisoned red corpuscles which the control animals possessed in their spleen. As would be expected, following splenectomy, animals succumb after loss of smaller amounts of blood than do the normal controls.

The corpuscles in the splenic pulp are *more fragile* than those in the general circulation. Most of them lake in 0·65 to 0·6 per cent. saline compared with 0·45 per cent. for the cells of the general circulation.

4. **Metabolism of Iron.**—The spleen probably plays a dominant rôle in the metabolism of iron, which may be conveniently considered here:

The amount of iron found in the red cells is about 3 grm., and another 1 to 3 grm. are present in the general tissues of the body, chiefly in the chromatin of the nuclei. Iron enters the body chiefly in animal food and in the chlorophyll of green vegetables. Only 5 to 10 mg. of iron are present in the ordinary dietary and even less may be sufficient to maintain the iron equilibrium. It is absorbed from the duodenum and the upper part of the small intestine. A portion is used for the purposes of the body and the excess is excreted by the large intestine in the fæces, and to a minor extent by the kidney. It is not known whether the epithelial cells of the intestine or the leucocytes are chiefly responsible for the absorption of iron, which is probably carried in the blood stream to the liver, where it may be temporarily stored. At birth the body of the fœtus is rich in stores of iron which it has obtained from the mother. As milk contains practically no iron, a fall in the iron content of the body occurs during suckling, but this is recovered from when an ordinary mixed diet begins to be taken. As iron is an essential constituent of hæmoglobin and probably plays an important part in the oxidative processes in the tissues, one would expect iron deprivation to be followed by serious effects. If an iron-free diet is given to mice they become

anæmic and their rate of growth is diminished. This experiment may be continued over successive generations, leading to the production of meagre, stunted animals. If to one of the litters an adequate iron-containing diet is given, the hæmoglobin content of the blood is quickly restored to the normal level, and rapid growth of the body as a whole occurs.

It is doubtful whether iron deprivation plays much part in disease. *Chlorosis* is a condition in which the red cell count per c.mm. is lowered and the individual corpuscles are deficient in hæmoglobin, and the disorder is very readily cured by the administration of iron. But the essential pathology of the disease is very obscure. There is probably no shortage of red cells, but the total blood volume is increased for some unknown reason and thus the number of corpuscles per unit of blood is diminished. The disease has now become quite rare, but why it is disappearing or why iron cured the condition is not definitely known.

As a result of the blood destruction which is always going on in the body, free iron is formed and is retained in the spleen and marrow. We do not know how this iron is disposed of. Possibly the iron-containing cells pass into the blood stream and disintegrate there. The freed iron may then be carried to the bone marrow to be used in the formation of fresh hæmoglobin. Some iron is certainly taken up and stored in small amounts in the liver cells, for free iron can be demonstrated in small amounts in the hepatic cells, but its rôle there is obscure.

In states of excessive blood destruction the spleen and reticulo-endothelial system generally become overfilled with iron, and then considerable deposition of the excess iron is found in the hepatic cells. If large amounts of hæmoglobin are injected into animals over a prolonged period, deposition of iron (*hæmosiderosis*) occurs first in the spleen, lymph nodes, and bone marrow, but later it appears in the liver, kidneys, salivary glands, and finally even in the heart muscle. In *toxic hæmolytic jaundice* similar findings obtain. In *pernicious anæmia* the liver and kidney are markedly hæmosiderosed and give the Prussian blue reaction for iron very readily.

In *familial hæmolytic* (*acholuric*) *jaundice*, however, in which there is abnormal fragility and consequently excessive destruction of red corpuscles, no significant increase in the deposition of iron is said to occur.

Following splenectomy, the storage of iron is interfered with and increased excretion occurs *via* the kidneys. The Kupffer cells proliferate and become increasingly infiltrated with iron, and some iron may actually be excreted by the hepatic cells into the bile. If iron is administered by the mouth, the excessive excretion by the kidneys is particularly well marked.

Hæmochromatosis is a disease in which there is an extraordinary deposit of iron in all the organs, chiefly in the form of hæmosiderin. An iron-free pigment—hæmofuscin—is also deposited. The iron is chiefly found in the reticulo-endothelial system, but is also present in the parenchyma of the liver, pancreas, and other organs, where it acts as an irritating foreign body causing secondary fibrosis. There is no evidence whatever of excessive blood destruction, so the essential nature of the disease remains a mystery. Possibly there is *defective excretion* of iron in the large intestine, with consequent retention in the body and deposition in various organs.

5. **Metabolism of Fat.**—Many lipoids are stored in the reticulum cells of the spleen. This is especially seen when the blood cholesterol is high, as in

diabetes or after excessive ingestion of this substance. (Cholesterol may also be deposited in certain connective-tissue cells in the skin, which are closely related to the reticulo-endothelial system, and form tumour-like proliferations of a yellow colour—so called *xanthelasma*).

6. **Defence Reactions.**—There is little doubt that the spleen is actively concerned in forming *hæmolytic* antibodies under experimental conditions. If the reticulo-endothelial system is poisoned by injection of collargol, the amount of *immune* bodies formed by the animal is diminished. Splenectomized animals cannot be immunized against tetanus toxin, and these animals succumb much more readily to intercurrent infections than do the controls. The splenic cells unite readily with diphtheria toxin and retain it, and thus prevent it from exerting harmful effects on the body as a whole. Bacteria injected intravenously are taken up with great rapidity by the reticulo-endothelial system, which is also concerned with engulfing larger parasites, like those of kala-azar. The system reacts too in many subacute and chronic infections. It is well known that in typhoid fever the sinuses of the lymph glands and the splenic pulp are packed with mononuclear cells. It is clear that the spleen and reticulo-endothelial system generally play an important part in the defence processes of the body

Extirpation of the Spleen.—From the facts already brought forward, it appears that though the spleen is not essential to life it has many important duties to perform. Other parts of the body take over as far as possible the functions of the lost organ, but presumably the body is considerably handicapped without a spleen.

After splenectomy in normal animals, the most obvious effects are :

1. An *anæmia* of the secondary type, mild or moderate in character, which usually reaches its severest stage after one and a half months and is followed by slow and steady recovery during the succeeding three or four months. The red count rarely falls below 3,000,000 per c.mm. or the hæmoglobin below 55 per cent. It is not usual for immature or nucleated red cells to appear after experimental splenectomy, but many such forms appear in the circulation after removal of the spleen for anæmia in the human subject (" blood crisis ").

The cause of the anæmia is uncertain, but it may be due to the removal of the store of corpuscles and of iron present in the spleen.[1] It is later compensated by overgrowth of the red bone marrow. The other functions of the spleen are taken over by the various portions of the reticulo-endothelial system. As the reserves of oxygen-carrying capacity have been lost, hæmorrhage is less well tolerated and possibly less exercise can be indulged in, explaining the asthenia that may be complained of after splenectomy. The red cells after splenectomy are said to be *more resistant* to the hæmolytic action of hypotonic saline solutions. The number of blood *platelets* is increased temporarily.

2. There is an increase in the total number of leucocytes, perhaps to 20,000 to 40,000 per c.mm. This is almost entirely due to the increase in the number of polymorphs. The white corpuscle count returns to normal very slowly. Later the lymphocytes may show a slight increase. Eosinophilia is an inconstant occurrence.

[1] Krumbhaar believes that the spleen gives rise to some substance which normally stimulates the marrow to activity.

Splenectomy has been advised in the following conditions :

1. *Acholuric jaundice*, in which, for some unknown reason, the red blood corpuscles are excessively fragile (p. 196) ; the spleen is enlarged and the pulp is packed with cells. If the spleen is removed, the destruction of red cells in excessive amounts ceases, and the resulting jaundice is arrested. It is said that the resistance of the red cells to hypotonic saline returns to normal after splenectomy has been performed for this condition.

2. *Banti's Disease.*—This disease and the analogous splenic anæmia of children have been regarded in the light of "hypersplenism" or over-functioning of the reticulo-endothelial system, which thus produces the characteristic anæmia. The spleen in Banti's disease is fibrosed and empty of cells, rather negativing the above view. It is more likely that the disease is due to a chronic infection localized in the spleen, and splenectomy cures the condition by removing the focus of infection.

3. *Pernicious anæmia* was sometimes treated in the past by splenectomy, but the disease is now controlled by dietetic measures (p. 205).

4. *Purpura hæmorrhagica* (see p. 211) : some cases of this malady have been cured by splenectomy.

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The Reaction of the Blood and Neutrality Regulation in the Body.—Recent investigations have shown that the reaction of the blood and tissues of the body is preserved at a fairly constant level by a series of delicate mechanisms, and that wide variations from the normal are incompatible with life. The actual methods employed by the body to achieve this end are rather complicated, but before we can deal with them there are certain general considerations that we must study.

Pure water consists almost entirely of molecules of H_2O ; but in addition a few molecules have dissociated to give rise to hydrogen ions and hydroxyl ions. An ion is an electrically charged particle, the H ions being charged with positive electricity and the OH ions with negative electricity. The reaction of any fluid depends on the relative number of H and OH ions. If there is an excess of H ions the solution is acid, and if the OH ions are in excess the solution is alkaline. Pure water is a perfectly neutral solution, and the H and OH ions are therefore equal in number. It has been possible actually to estimate the number of ions in pure water.[1] The concentration of ions is expressed in terms of *gramme equivalents per litre* of the solution. The concentration of H ions $=[\overset{+}{H}]$ is 10^{-7} in the case of pure water at 22° C. 10^{-7} means $\frac{1}{10^7}$ or $\frac{1}{10 \text{ million}}$ and $[\overset{+}{H}]=10^{-7}$ means there is 1 grm. equivalent of hydrogen in the ionic form in 10 million litres of water. The equivalent weight of H is one, so there is 1 grm. by weight of ionic hydrogen in 10 million

[1] cH and cOH mean concentration of H ions and of OH ions respectively. The symbols $[\overset{+}{H}]$ and $[\overset{-}{OH}]$ mean that the concentration of H and of OH ions are being expressed in terms of gramme-equivalents of the ion per litre of the solution.

litres of water. As the number of OH ions is the same as that of H ions, $[\bar{O}H]$ is also 10^{-7}, or 1 grm. equivalent of OH in the ionic form is present in 10 million litres of water. The equivalent weight of OH (O=16, H=1) is 17, so the actual *weight* of ionic OH is 17 grm. in 10 million litres of water; but the *number* of OH ions (and that is all that concerns us) is identical with the number of H ions.

It is further found that if $[\dot{H}]$ is multiplied by $[\bar{O}H]$, the product is constant for *all* solutions, whatever their reaction may be. In the case of pure water we know the data

$$[\dot{H}]\times[\bar{O}H]=10^{-7} \times 10^{-7} = 10^{-14}$$
$$=\frac{1}{10 \text{ million}}\times\frac{1}{10 \text{ million}}=\frac{1}{100 \text{ million million}}.$$

It follows from this that if we merely know the $[\dot{H}]$ of any solution, we can deduce the $[\bar{O}H]$, as the product of the two must be 10^{-14}. We can then compare the H ion and OH ion concentration, see which is greater, and thus we know the reaction of the fluid. To take an example:

If the H ion concentration is 10^{-6} (1 in a million)
as $[\dot{H}]\times[\bar{O}H]=10^{-14}$ (1 in a 100 million million)
$\therefore [\bar{O}H]=10^{-8}$ (1 in a 100 million)

Clearly the concentration of H ions is 100 times as great as the concentration of OH ions, and therefore the solution is strongly acid.

$\therefore [\dot{H}]=10^{-7}\ [\bar{O}H]=10^{-7}$=neutral solution.
$[\dot{H}]=10^{-6}\ [\bar{O}H]=10^{-8}$=acid solution.
$[\dot{H}]=10^{-8}\ [\bar{O}H]=10^{-6}$=alkaline solution.

Note that *lowering* the size of the index *increases* the concentration, 10^{-6} (1 in a million) being a greater concentration than 10^{-8} (1 in a 100 million). A *normal* solution of an acid or base is one which contains the equivalent weight (of the acid or base) expressed in grammes in 1 litre of the solution. A strong acid dissociates freely, and so all the H present is found in the ionic form, and similarly a strong base contains all its OH in the ionic state. In the case of HCl the equivalent weight is 36·5, so that a normal solution contains 36·5 grm. HCl per litre. A normal solution contains 1 grm. of H per litre, all in the ionic state. $\therefore [\dot{H}]$ of a normal solution=1 [of a decinormal solution it is 10^{-1}, etc.]. In a normal solution in which, as stated, $[\dot{H}]=1$, [OH] must be 10^{-14}, *i.e.* the number of OH ions is very low. The presence of the strong acid has depressed the ionization of water, of which only an infinitesimally small fraction is in the ionic state.

To avoid the negative indices of the cH method, Sørensen has introduced a

new nomenclature, that of *p*H. *p* is an arbitrarily chosen letter to signify that the negative exponent to the base 10 is employed.

Thus if $cH=10^{-7}$, *p*H=7.
if $cH=10^{-6}$, *p*H=6.
if $cH=10^{-8}$, *p*H=8.

(The index is used and the minus sign removed.) When faced with the *p*H of a fluid it is a little difficult at first to see what it signifies. It is perhaps best to translate into terms of cH, which are more readily grasped. Thus—

*p*H=7, $cH=10^{-7}$=neutral solution.
*p*H=6, $cH=10^{-6}$=acid solution.
*p*H=8, $cH=10^{-8}$=alkaline solution.

Thus if the *pH exceeds 7, the solution is alkaline*, if it is *less than 7 it is acid.*

Certain terms must now be defined :

Reaction of the Blood.—By blood is meant plasma as it exists normally in contact with red corpuscles, and exposed to the normal CO_2 tension of the blood (40 mm. Hg in arterial blood). The reaction is the degree of acidity or alkalinity as determined by the H ion concentration.

Acidæmia.—Increased H ion concentration of blood beyond the normal limits.

Alkalæmia.—Diminished H ion concentration below normal limits.

Ketosis is a new term introduced to avoid much of the misunderstanding hitherto prevalent. Under certain conditions, abnormal fatty acids appear in the blood and urine, namely :

β oxy-butyric acid, $CH_3CHOH\ CH_2COOH$.
Aceto-acetic acid, CH_3COCH_2COOH.

It has been customary to call this state " acidosis," which implies an increased H ion concentration. Actual measurement often fails to reveal any increased cH of the blood, because of the perfect compensatory processes brought into play by the body. " Acidosis " is therefore abandoned in favour of " ketosis," which simply implies the presence of these abnormal acids in the blood, and does not give any information about the actual H ion concentration.

Alkali reserve (Van Slyke) does not, as the name implies, refer to all the stores of alkali in the blood. Roughly speaking, it is the *bicarbonate content* of the blood, as will appear from its method of determination. CO_2 is present in blood, to a slight extent in solution, but principally combined with base as bicarbonate (cf. p. 347). Blood is brought into equilibrium with alveolar air (CO_2 tension=40 mm. Hg) at room temperature, and the CO_2 present is expelled by means of acid and measured. The amount known to be in solution is deducted, the rest of the CO_2 (which was in combination) expressed dry, and at normal temperature (0° C.) and pressure (760 mm.) (N.T.P.), in volumes per cent. represents the alkali reserve. If the total volume of CO_2 given off in the vacuum were 52·5 c.cm. of which 2·5 c.cm. is calculated as being in solution, the alkali reserve is 50 volumes per cent. It is suggested that the term *fixed CO_2* of the blood at an agreed CO_2 pressure and temperature would be a more suitable expression to employ than " alkali reserve."

Buffer substances are those which hinder changes in the reaction of a fluid. The word is derived from a German word meaning tampon, a buffer substance being regarded as " mopping up " H or OH ions and thus preventing them from accumulating. The mode of action of buffers will be made clear shortly.

The chief acid of the blood is H_2CO_3 (or CO_2 in solution), which gives rise to H ions thus :

$$H_2O+CO_2 \rightleftarrows H_2CO_3 \rightleftarrows H^+ + HCO_3'.$$

The base of the blood is the bicarbonate (or CO_2 in combination), which dissociates thus :

$$H_2O+NaHCO_3 \rightleftarrows Na^+ + H_2CO_3 + OH'$$
$$\Downarrow\Downarrow$$
$$H^+ + HCO_3'.$$

The H_2CO_3 formed in the equation dissociates very *slightly,* so but few H ions are formed. The number of OH ions liberated are more numerous.

As the reaction of the blood depends on the ratio of H and OH ions it may be expressed thus :

$$\text{cH varies as } \frac{H_2CO_3}{NaHCO_3}.$$

Acidæmia can be due to increase in the H_2CO_3 or diminution of the bicarbonate ; *alkalæmia* to a fall in the H_2CO_3 or an increase in the bicarbonate. A normal reaction will be found if both H_2CO_3 and bicarbonate increase or diminish proportionately.

The definitions given above are those recommended by the Medical Research Council, but unfortunately American usage is somewhat different.

Measurement of H Ion Concentration.—Since it is the arterial rather than the venous blood which supplies the tissues generally, it is more strictly accurate to use samples of that blood for all determinations. Specimens can be obtained with safety from the radial artery by puncturing it with a hypodermic needle if a proper technique is employed. Venous blood can be obtained with greater ease from the arm veins in adults, or the sagittal sinus in infants, but does not necessarily represent the mixed venous blood or the venous blood in other regions of the body. Theoretically it should be possible to reconstruct arterial from a sample of venous blood by exposing it to the appropriate CO_2 and oxygen tensions. In practice the process is not successful. Blood must be employed fresh, and clotting prevented by addition of potassium oxalate.

The most reliable method is to employ the *hydrogen electrode.* The technique is difficult and the principle is complicated, and as fairly reliable comparative results can be obtained by the use of the *indicator* method, which is easier to employ, that method alone will be described (Dale and Evans).

A collodion sac holding 2 to 3 c.cm. is completely filled with oxalated blood which is allowed to dialyse into 1 c.cm. of 0·8 per cent. NaCl solution, contact with air being prevented. In this way a dialysate is obtained in which the ratio of free to combined carbon dioxide is the same as in blood plasma. After twenty minutes, a clear and colourless dialysate is obtained to which some indicator like *neutral red* or phenolsulphone-phthalein is added in measured amount. The tint is then matched against that of phosphate

solutions of known *p*H treated with the same indicator, and the reaction thus determined.

The normal limits of H ion concentration by the indicator method are *p*H 7·72 to 7·64 ; by the hydrogen electrode method, 7·47 to 7·34, *i.e.* somewhat less alkaline readings.

Acids are constantly being formed in the body as a result of metabolic activity. CO_2 results from the oxidation of all food-stuffs ; H_3PO_4 and H_2SO_4 from the oxidation of the P and S of ingested protein. Lactic acid is formed in the muscles during activity, but normally it is removed as rapidly as it appears. In very strenuous exercise, especially under conditions of oxygen-lack, lactic acid may be formed in greater amounts than the muscles can deal with, and it consequently overflows into the blood. Under abnormal conditions β-oxy-butyric acid, aceto-acetic acid, and possibly other acids not hitherto recognized may appear in the circulation.

Basic radicles like Na, K, Ca, Mg are taken in large amounts in an ordinary diet, especially in vegetable food, and they must be disposed of to prevent excessive alkalinity of the blood.

It is therefore remarkable that the blood-reaction is kept so very constant under physiological conditions. Measurable alterations in the H ion concentration do occur, however, even in health : a definite acidæmia is obtained in severe exercise and an alkalæmia in rarefied atmospheres. In disease greater deviations can be demonstrated (*p*H 7·95 to 7·36 by indicator method). The extreme limits of H ion concentration compatible with life in experimental animals are *p*H 9 to 7·22.

The methods available in the body for maintaining blood reaction are the *physico-chemical* processes occurring in the blood, and the *vital* reactions of the respiratory centre, the liver, and the kidneys.

I. **Physico-Chemical Reactions.**—1. If any non-volatile acid like lactic, phosphoric, or sulphuric acid enters the blood stream, it at once interacts with the bicarbonate present in the plasma as follows :

$$\underset{\text{(Lactic acid.)}}{HL} + \underset{\text{(Sodium lactate.)}}{NaHCO_3} \rightarrow NaL + H_2CO_3.$$

(i)

In the case of lactic acid, sodium lactate and carbonic acid are formed. The advantage of this reaction to the body is clear. Lactic acid is a strong acid, which means an acid which dissociates freely and gives rise to many H ions, and thus makes any solution in which it is present very acid ; it is also a non-volatile acid which is excreted slowly in the urine. By the interaction with sodium bicarbonate it is converted into a neutral salt and H_2CO_3 is liberated. Now H_2CO_3 is a much weaker acid, giving rise to fewer H ions ; furthermore, it is a volatile acid which is readily eliminated in the lungs. Sodium bicarbonate has therefore acted as a *buffer* substance ; it has caused H ions to be " mopped up," fewer are left in the solution, and the reaction of the blood has altered to a much slighter extent than otherwise would have been the case. That is why the term " alkali reserve " was introduced to describe the bicarbonate of the blood.

It follows that as long as $NaHCO_3$ is present in the plasma, no acid stronger than carbonic can exist in the blood as such.

2. But the acid formed in largest amounts in the body is H_2CO_3 itself,

which of course cannot be dealt with by $NaHCO_3$. H_2CO_3 is dealt with in the following way:

(ii) $H_2CO_3 + NaCl \gtrless NaHCO_2 + HCl$.

(iii) $HCl + KHb \gtrless KCl + HHb$.

(Potassium salt of reduced hæmoglobin.)

H_2CO_3 interacts with the sodium chloride of the plasma to form sodium bicarbonate and hydrochloric acid. On the face of it this reaction seems both meaningless and impossible. Instead of the weak acid H_2CO_3, we have formed the stronger acid HCl, so the H ion concentration of the solution ought to rise still higher. Again, a weak acid like H_2CO_3 cannot displace chloride from its union with Na in NaCl. The explanation is this. An equation like (ii) above can act in either direction if the product of the reaction that would tend to drive the process the opposite way is at once removed. In other words, the equation will go from left to right if the HCl formed is at once removed from the plasma. This actually happens. If blood is exposed to increased tensions of CO_2, the amount of $NaHCO_3$ in the plasma increases and the chloride diminishes in the plasma and increases in the interior of the red blood corpuscles. The HCl resulting from Equation ii., as it is formed in minute amounts, migrates rapidly through the corpuscular wall to be dealt with suitably in the red cell. This is the *Hamburger* phenomenon, or *chloride shift*.

The proteins of the blood can act either as weak acids or as weak bases.[1] As blood is an alkaline solution they act as weak acids and are therefore found combined with certain basic radicles. The plasma proteins are chiefly united with Na, the substance formed being represented diagrammatically as NaPr. When the proteins lose their base they can be written as HPr, the H denoting their acid character. The hæmoglobin of the corpuscle is combined principally with potassium and is therefore written as KHb or $KHbO_2$ (the potassium salt of reduced and oxy-hæmoglobin respectively). The proteins of the blood are therefore storehouses of base, which can be taken from them by any acid strong enough to do so. Thus when HCl enters the corpuscle it interacts with the potassium hæmoglobinate present there to form KCl and leave the hæmoglobin containing less base—diagrammatically represented as HHb (Equation iii.).

A further point must be considered. Hæmoglobin exists in the blood in an oxidized and reduced form. It has been shown that oxy-hæmoglobin is a much *stronger acid*, perhaps seventy times as strong as reduced hæmoglobin. It is much easier to take base from the salt of a weak acid. CO_2 is formed in the tissues during activity, when much oxygen is being used. Therefore when CO_2 is diffusing into the blood to form H_2CO_3. the reduced hæmoglobin is chiefly present, which gives up base readily, so that Equation iii. is facilitated.

3. H_2CO_3 also obtains base from the protein of the plasma, $NaHCO_3$ being formed.

(iv) $H_2CO_3 + NaPr \gtrless NaHCO_3 + HPr$.

(Sodium proteinate.)

[1] See footnote, p. 159. The iso-electric point of plasma proteins is *p*H 4·7, that of oxy-hæmoglobin is *p*H 6·75.

The proteic acid, *e.g.* HPr, is a very weak acid and dissociates very feebly, so again there is a net removal of H ions.

H_2CO_3 diffuses into the interior of the red cell and obtains base directly from hæmoglobin.

$$\text{(v)}\ H_2CO_3 + KHb \rightleftarrows KHCO_3 + HHb.$$

It has been estimated that 84 to 90 per cent. (Van Slyke) of the base required to deal with H_2CO_3 is supplied directly or indirectly by the hæmoglobin. It is true in Equation ii. the base is obtained from NaCl, but we saw the reaction could not occur if it were not for the fact that the HCl was subsequently buffered by hæmoglobin. It is therefore fair to say that hæmoglobin is ultimately responsible for the base supplied in Equation ii. The serum proteins only constitute 8 per cent. of the plasma (compared to 30 per cent. of hæmoglobin in the corpuscles), and their buffering action is relatively unimportant. Whole blood is therefore much more effectively buffered than plasma alone. If the corpuscles are diminished in number, as in anæmia, the H ion concentration tends to rise excessively when CO_2 enters the blood.

It will be noticed that in an equation like (v) $H_2CO_3 + KHb \rightleftarrows KHCO_3 + HHb$, H_2CO_3 disappears and is replaced by bicarbonate, which is actually an *alkaline* substance giving rise to an excess of OH ions. The hæmoglobin formed, like all proteins, is a weak acid which dissociates very feebly. The buffering reaction is therefore extremely effective.

4. As already explained, H_2CO_3 is dealt with first by hæmoglobin, then by the plasma proteins, and only in the last resort and to an unimportant extent by the phosphates, which are only present in sufficiently high concentration in the corpuscles.

$$\text{(vi)}\ H_2CO_3 + Na_2HPO_4 \rightleftarrows NaHCO_3 + NaH_2PO_4.$$

The alkaline sodium phosphate Na_2HPO_4 gives up some of its base to H_2CO_3 to form bicarbonate, and is itself converted into NaH_2PO_4, which is very feebly acid.

The equations given represent what occurs when H_2CO_3 is accumulating in the blood, and show how the expected acidæmia is minimized. When CO_2 is given off in the lungs, the processes will take place in the reverse direction, preventing excessive alkalæmia. It is convenient to gather the various equations together. The hæmoglobin is now in the more acid oxidized form, and will be written as HbO_2 and $KHbO_2$ to indicate this.

(iii) $HHbO_2 + KCl \rightleftarrows KHbO_2 + HCl$ (corpuscle).
(ii) $HCl + NaHCO_3 \rightleftarrows NaCl + H_2CO_3$ (plasma).
(iv) $NaHCO_3 + HPr \rightleftarrows NaPr + H_2CO_3$ (plasma).
(v) $KHCO_3 + HHbO_2 \rightleftarrows KHbO_2 + H_2CO_3$ (corpuscle).
(vi) $NaH_2PO_4 + NaHCO_3 \rightleftarrows Na_2HPO_4 + H_2CO_3$ (corpuscle).

We shall have to point out (cf. p. 350) that not only do these equations represent buffering actions tending to maintain normal blood reaction, but they also explain how CO_2 is carried in the blood. The problem of CO_2 carriage is how base is obtained to form bicarbonate in the tissues and how that bicarbonate is decomposed and CO_2 liberated in the lungs. How these equations explain this matter is discussed on pp. 349–351.

II. Vital Reactions.—1. Respiratory Centre.—We shall see (p. 317) that one of the purposes of the breathing is to maintain the normal blood reaction. The respiratory centre can detect changes in cH very promptly and much more delicately than our most accurate physical instruments. If the H ion concentration of the blood tends to rise, the pulmonary ventilation is increased, more fresh air is taken into the lungs, more CO_2 is eliminated, and the level of the alveolar CO_2 is lowered. The alveolar CO_2 tension regulates the amount of H_2CO_3 in the arterial blood, so that a fall of alveolar CO_2 means a lowered arterial CO_2 and H_2CO_3 content and therefore a lower H ion concentration. The tendency to acidæmia which initiated these changes is thus combated. Similarly when the H ion concentration of the blood tends to fall, the pulmonary ventilation is diminished, CO_2 is retained, the alveolar CO_2 consequently rise, the arterial CO_2 and H_2CO_3 rise, and the

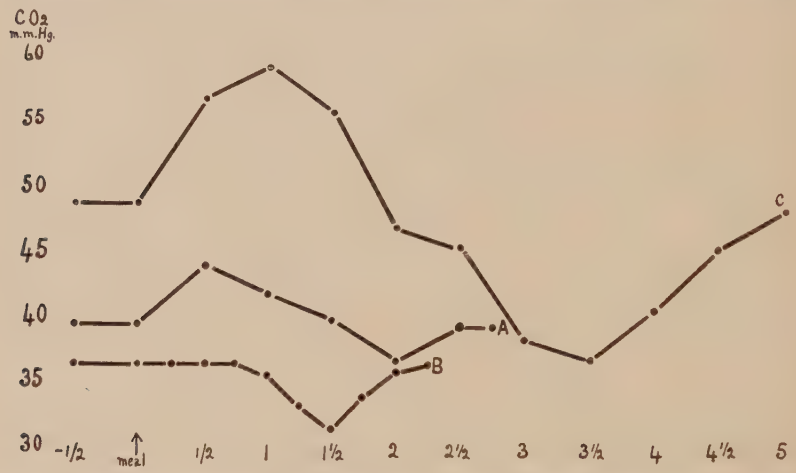

Fig. 64.—Changes in Alveolar CO_2 Tension with Meals. Abscissa = time in hours; ordinate = CO_2 tension in mm. Hg.

A = Normal subject; B = Healthy subject with complete achylia gastrica; C = Case with marked hypersecretion of gastric juice. (Dodds and Bennett, *Journ. Physiol.*, 1921.)

H ions in the blood are increased and the normal condition is restored. The matter is more fully dealt with on p. 321.

2. The Kidney.—The kidney can modify the reaction of the urine by excreting varying proportions of the acid phosphate (NaH_2PO_4) and alkaline phosphate (Na_2HPO_4). When there is a tendency to acidæmia the acid phosphate is excreted, the blood thereby being made more alkaline, and the reverse occurs when there is a tendency to alkalæmia. An alkaline urine is then formed, and more basic substances are thus eliminated from the blood. The ordinary mixed diet being potentially acid-forming, the kidney responds by excreting an acid urine. The kidney is less sensitive than the respiratory centre in its recognition of alterations in blood reaction. Though there may be some delay before the kidney comes into action, it constitutes an extremely important compensatory mechanism (cf. p. 470 and Fig. 65).

3. The Ammonium Mechanism.—Amino-acids are absorbed from the

small intestine and undergo de-amination in the liver. The NH_3 thus liberated is available for union with acid radicles. It is seized first by the strong acid radicles to form ammonium salts which are excreted in the urine. The rest of the NH_3 combines with carbonic acid to form ammonium carbonate, which is converted into urea and excreted as such. In acidæmia there is an excess of acid radicles or a relative deficiency of the fixed bases of the blood to combine with them. More of the NH_3 is used to combine with fixed acid radicles, and the ammonium excretion in urine goes up. In alkalæmia there are less acid radicles or a relative excess of the base. So less of the NH_3 is called upon, and the ammonium excretion diminishes. This is the generally accepted view, but recently Nash and Benedict have shown that ammonia is manufactured by the renal cells themselves in amounts which will depend on blood reaction; the blood in the renal vein contains a larger amount of ammonium than that in the renal artery (cf. p. 466). In acidæmia more NH_4 is made and in alkalæmia less. The urinary ammonium is often referred to as "ammonia," and this is confusing, for in acidæmia there is more urinary "ammonia," but of course a highly acid urine.

An example will perhaps make clearer the general statements made above. In most normal people HCl is poured out into the stomach during gastric digestion. Exactly how the acid is formed is not certain and does not concern us at the moment, but it must be derived from blood constituents, and tends to produce an alkalæmia. Similarly, during pancreatic secretion Na_2CO_3 is formed and a tendency to acidæmia must develop. Dodds showed that during gastric secretion the alveolar CO_2 rises, and during pancreatic secretion it falls below normal. In the accompanying table the various reactions of the body are summarized, the hypothetical changes being represented in italics :

Gastric Secretion—	Pancreatic Secretion—
HCl eliminated.	Na_2CO_3 eliminated.
Tendency to alkalæmia—	Tendency to acidæmia—
Respiratory centre depressed.	*Respiratory centre stimulated.*
Pulmonary ventilation diminished.	*Pulmonary ventilation increased.*
Alveolar CO_2 rises.	Alveolar CO_2 falls.
Arterial CO_2 rises.	Arterial CO_2 falls.
Less acid urine.	More acid urine.
Less NH_4 in urine.	More NH_4 in urine.

The rise of alveolar and arterial CO_2 tension during gastric secretion increases the H_2CO_3 of the blood, and consequently its H ion concentration, and compensates for the loss of H ions in the HCl of the gastric juice. Dodds and Bennett found that the rise of alveolar CO_2 runs parallel with gastric acidity (see Fig. 64). [In achlorhydria, in which no free HCl is formed, the alveolar CO_2 does not rise.] Further, the urine is less acid and thus again H ions are conserved in the body. Less NH_4 is excreted, the fixed acids being combined with the fixed base of the blood, and thus more of that base is eliminated from the body, again raising the H ion concentration. Just the reverse occurs during pancreatic secretion. Compensation is so perfectly achieved that direct measurement fails to reveal any alteration in blood reaction with meals. The urinary changes described are best seen after the first meal of the day. For the first two hours there is less acid and less NH_4 in the urine (*alkaline tide*), and in the succeeding two hours the

response to pancreatic secretion gives a more acid urine and a higher NH_4 content. Similar changes follow the succeeding meals, but are not so clear cut, because the response to the first meal obscures and overlaps the changes induced by the next meal (Dodds).

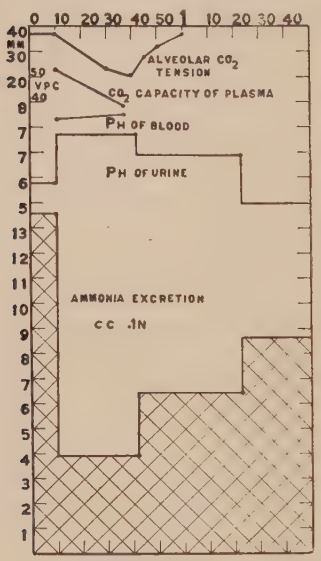

FIG. 65.—Effect of Voluntary Hyperpnœa on Alveolar Air, Blood, and Urine, shewing compensatory reactions to alkalæmia.

Abscissa = Time in minutes. Alveolar CO_2 tension in mm. Hg. CO_2 capacity of plasma (bicarbonate content) in volumes of CO_2 per 100 c.cm. plasma. Reaction of blood and urine expressed as *p*H; rise means increased alkalinity. "Ammonium" of urine in c.cm. of decinormal solution. Forced respiration begins at 10 mins. and ends at 38 mins. At 31 mins., tingling in foot; at 34 mins., Trousseau's sign present; at 35 mins., both hands in spontaneous spasm; at 36 mins., slight spasm of feet (see pp. 160, 162); at 42 mins., temporary dizziness and trembling of hands on standing up after period of forced respiration is over. Note that *p*H of blood rises in spite of compensatory reactions of kidney. (Grant and Goldman, *Amer. Journ. Physiol.*, 1920.)

In severe muscular *exercise* an acidæmia occurs (see p. 362). Marked changes in the H ion concentration of the blood are not compatible with life. Any tendency to alkalæmia or acidæmia is at once combated by the various means at the disposal of the blood. It is only when these compensatory mechanisms fail or become inadequate that changes occur in the reaction of the blood which can be detected by the physical methods at our disposal.

Alkalæmia.—In the following conditions there is a tendency to alkalæmia. In more severe cases the altered blood reaction may be demonstrable.

1. Excessive breathing at rest which washes out an excessive amount of CO_2 from the alveolar air and lowers the CO_2 tension in the arterial blood. This may be due to: (i) Voluntary hyperpnœa (Fig. 65); (ii) exposure to high external temperature, especially when the air is moist—the respiratory centre is stimulated by the raised temperature of the blood (p. 378); (iii) anoxæmia stimulating the respiratory centre (see p. 324), *e.g.* at high altitudes, in cardiac failure (p. 372). The kidney endeavours to compensate for the alkalæmia by excreting urine which contains less ammonium and more alkali phosphate (Fig. 65).

2. Increase in the bicarbonate content of the blood. This occurs in (i) ingestion of overdoses of bicarbonate. (ii) Pyloric obstruction; this has been attributed to loss of hydrochloric acid from the body in the vomit, but alkalæmia may develop when the obstruction is due to carcinoma, in which case achlorhydria is usually present, *i.e.* no secretion of HCl at all. The cause of the alkalæmia is therefore not finally decided. (iii) High intestinal obstruction; it is suggested that a toxic body develops above the obstruction which combines with the chloride part of the plasma NaCl. Excess of base is thus left over to combine with CO_2 to form bicarbonate (p. 411). It has already been pointed out (p. 161) that alkalæmia probably diminishes the amount of calcium in ionic form in the blood and so predisposes to tetany.

Acidæmia.—Acidæmia may be present owing to diminution of the bicarbonate content of the blood or increase in the H_2CO_3 of the blood.

1. i. The ingestion of wood spirit, *i.e.* methyl alcohol, gives rise to formic acid in the body (p. 370).

ii. Ammonium chloride after absorption is de-aminized in the body: NH_3 is split off and HCl is left, which enters the blood (p. 322).

iii. In starvation and in diabetes fat metabolism stops short at the stage of β-oxybutyric and aceto-acetic acid (pp. 441, 419).

iv. In nephritis there is retention of a non-volatile acid (perhaps owing to defective elimination of phosphate by the diseased kidney) (p. 474).

In all these cases the bicarbonate content of the blood is lowered, as it is used to buffer the acids which have accumulated in the body. Increased pulmonary ventilation, lowered alveolar CO_2 tension, acid urine, and increased ammonium content are present. At first the "alkali deficit" is compensated, but later the H ion concentration may be demonstrably raised.

2. Excess of CO_2 in the blood occurs—

i. In experimental breathing of air containing increased percentages of CO_2 (p. 323).

ii. In morphine poisoning, owing to depression of the respiratory centre. The pulmonary ventilation becomes inadequate and so CO_2 is not eliminated in sufficient amounts. During *sleep* the alveolar CO_2 rises because of inadequate pulmonary ventilation; the urine is found to be highly acid (p. 330).

iii. In heart failure when the pulmonary epithelium is damaged so that CO_2 cannot diffuse out readily (p. 372).

iv. In emphysema, where the CO_2 tension in the alveolar air is raised. This is compensated for by an increased bicarbonate content of the blood (cf. p. 371).

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V

THE HEART

I

Structure—Special tissues—Origin and spread of impulse—Spread in auricle, bundle of His, ventricle—Human electro-cardiogram—Lævo- and dextro-cardiogram—Preponderance of ventricle—Extra-systoles—Heart block—Properties of heart muscle—Excitability and contractility—Refractory period—Conductivity—Law of cardiac muscle—Perfusion of the heart—Coronary circulation—Results of coronary occlusion—Movements of the heart.

1. Heart Muscle. — The fibres are transversely striated, but differ in certain important particulars from voluntary muscle. The striations are less distinct; the nucleus is situated centrally in the substance of the fibre; the fibres are cylindrical in shape and branch, uniting by means of their branches with adjacent cells. It is still doubtful whether definite cell membranes exist between the individual fibres, or whether heart muscle is to be regarded as a sheet of nucleated protoplasm (syncytium). It is probable that in all animals, at some stage of development, heart muscle consists of a syncytium, within which the contractile elements differentiate. It seems that only in the mammals do lines of demarcation definitely appear, and even these intervals between adjacent muscle cells are bridged over by intercellular fibrils. For all practical purposes there is functional continuity throughout heart muscle.

2. Special Tissues of the Heart.—This term is employed to describe certain tissues in the heart which are concerned with the initiation and propagation of the heart beat. They include the *sino-auricular node* and the *junctional tissues*—the latter consisting of the *auriculo-ventricular node*; the auriculo-ventricular bundle, or *bundle of His*; the right and left divisions of the bundle and their arborizations; and lastly the terminal fibres which penetrate the ventricular substance. The anatomy and histology of these tissues must now be described.

(*a*) Sino-Auricular Node.—This is situated at the junction of the superior vena cava and the free border of the right auricular appendix, and extends down along the sulcus terminalis for a distance of 2 cm. It is 2 mm. in width. The node has a special artery of supply which breaks up into a rich capillary meshwork. Nerve cells and fibres forming the excitor relay of the vagus nerve and excitor (post-ganglionic) fibres of the sympathetic are also present. The peculiar feature of the node is the presence of thin, elongated muscle fibres (about one-third the size of heart-muscle fibres), fusiform in shape and longitudinally striated, which interlace with one another in a plexiform manner. These modified muscle fibres are believed to initiate the

heart beat under normal circumstances, and for this reason the sino-auricular node is called the "pacemaker."

(*b*) Auriculo-Ventricular Node.—This is situated at the posterior and right border of the interauricular septum near the mouth of the coronary sinus. Auricular fibres from the region of the coronary sinus collect fanwise, interlace, and unite with the auriculo-ventricular node. In structure this node is identical with the sino-auricular node.

Morphology.—In amphibians and reptiles the great veins enter the sinus venosus, which forms a distinct chamber, separated from the auricle by a pair of venous valves. In mammals the sinus and auricle are fused together and a strict separation of the two structures is no longer possible. There is reason to believe that the sino-auricular node is a right-sided structure developing from tissue which lay at the entrance of the primitive right great vein

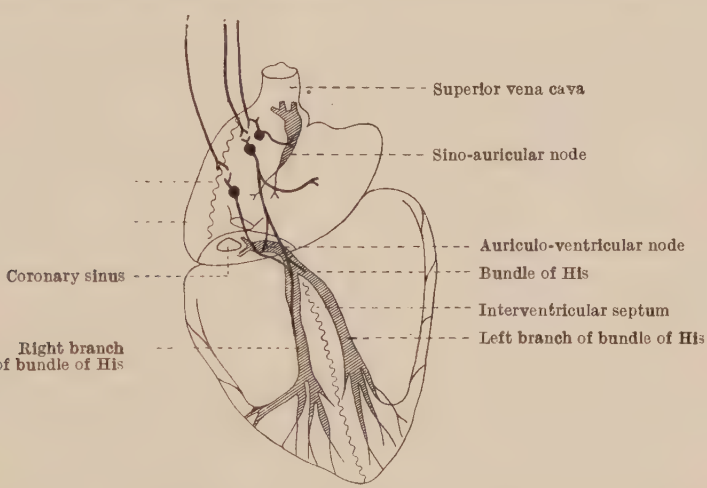

Fig. 66.—Diagram to show Arrangement of Special Tissue of Heart.—After Wiggers.

(which later becomes the superior vena cava). This explains the position of the node and its supply by the right vagus nerve. The auriculo-ventricular node is a left-sided structure, supplied therefore by the left vagus nerve, and developed from tissue in the vicinity of the entrance of the left great vein which becomes the coronary sinus. The anatomical position of the two nodes is thus also accounted for (Keith).

(*c*) The Bundle of His runs horizontally forwards and to the left to the pars membranacea septi, ensheathed and isolated in a canal. At the anterior part of the membranous septum, in front of the attachment of the septal cusp of the tricuspid valve to the A–V ring, the bundle forks. The *left* division pierces the membrane and then lies on the upper border of the muscular septum to enter the subendocardial space of the left ventricle beneath the union of the anterior and right posterior cusps of the aortic valve. This relation to the aortic valve is important, and explains how this branch of the bundle may be implicated in aortic incompetence. The *right* division

passes down the right side of the septum and enters the moderator band and the papillary muscles. Both branches are continuous with an arborization of fibres under the endocardium of both ventricles. These fibres are sometimes called the *fibres of Purkinje*. *Terminal fibrils* penetrate the ventricular wall.

The bundle of His is 1 to 2 mm. thick. Its fibres run parallel, are stout, and their striation is scanty. Their glycogen content is rich, and the bundle system can thus be well demonstrated by Best's carmine stain for this substance. The fibres increase in size in the divisions of the bundle and the striation becomes more imperfect. In the sheep and ox there is found a network of swollen fibres under the endocardium, with indistinct cell outlines, the nuclei large and often multiple, the protoplasm granular, and only striated at the periphery. These are the typical fibres of Purkinje, but they are not found in this characteristic form in the human heart. The vascular supply of the bundle and its branches is poor. The fibres which penetrate the ventricular wall become abruptly small, and more definitely striated longitudinally.

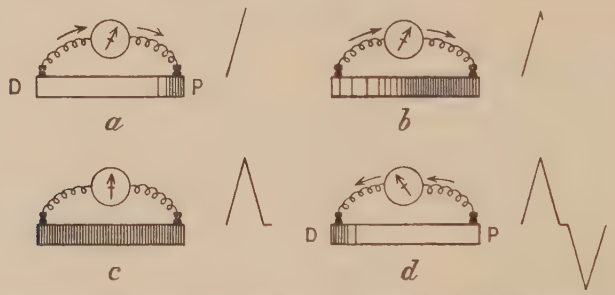

FIG. 67.—Diagram to illustrate the Spread of the Wave of "Negativity" in a Strip of Muscle, when stimulated at the end P. The shaded portion represents the region of negativity. The curve drawn by the deflection of the galvanometer at each stage is shown at the right (*a*, *b*, *c*, *d*).—After LEWIS.

Origin and Spread of the Cardiac Impulse.—Most of our knowledge of the spread of the cardiac impulse is derived from a study of the electrical variations arising in the beating heart, so we must consider in a general way the electrical changes occurring in a strip of a muscle under the simplest experimental conditions.

Non-polarizable electrodes are placed at each end of a strip of muscle and connected with a sensitive galvanometer. The point P is stimulated. The excitation process is initiated here, and as in the case of nerve (p. 13) the active region becomes relatively "negative" to the inactive part in the same sense as the zinc of a battery is negative to the copper, *i.e.* the current flows from the "positive" to the "negative" through the galvanometer, but in the reverse direction in the muscle. The "negative" point is therefore at a *higher electrical potential*, *i.e.* it is *electro*-positive. The galvanometer needle is deflected in a certain direction, and we will record it *upwards*. The excitation reaches D and for a moment both ends of the muscle are equally active, and so the galvanometer needle swings back to its original position; the two ends are iso-electric, and no current flows through the galvanometer.

The distal end of the muscle D persists for some moments in an active state, while the excitation process is subsiding at the proximal end P. D is now relatively " negative," and so the galvanometer needle swings in the opposite direction, which we record *downwards*. The excitation process passes off at D, the muscle becomes quiescent, and the galvanometer returns to rest. It will now be clear that the electrical curve obtained indicates the *direction* in which the excitation wave is travelling. Thus, had the impulse travelled from D to P, the first wave would have been downwards and the second upwards, *i.e.* in the reverse direction to that already noted when the wave travelled from P to D. As the curve shows two deflections it is called a *diphasic variation* (current of action), in contrast to the single deflection or uniphasic variation obtained when leading from an injured and normal spot on a muscle (current of injury) the injured region being " negative " compared to the healthy part.

The cardiac impulse arises in the sino-auricular node, spreads over the wall of the auricles, and thus reaches the auriculo-ventricular node. It then passes down the bundle of His and its branches and terminal ramifications, exciting the septum, apex, and base of the ventricles in that order. It is also necessary to point out that the naturally beating heart gives rise to a complex electrical variation (p. 233), the first upright deflection P being related to the excitation process in the auricle, while the later deflections QRST represent ventricular events.

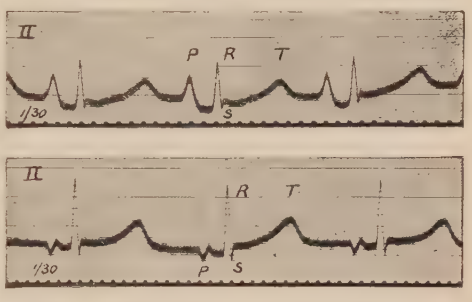

FIG. 68.—Two Electro-Cardiograms (Cat) taken immediately before and after Crushing the Region of the S.A. Node. In the lower figure the rate is slower and the auricular wave *P* is inverted instead of upright, indicating a change of pacemaker.—LEWIS.

The evidence for these statements can now be considered.

Sino-Auricular (S.A.) Node.—1. The sino-auricular node (or the " pacemaker ") initiates the normal heart beat. It would be expected, if it is the first part of the heart to be excited, that it should become " negative " before the other parts of the auricle. This is found to be the case, and points close up to the node become " negative " before the more outlying parts of the auricle.

2. The first deflection of the electro-cardiogram—the P wave—is believed to represent the invasion of the auricle by the excitation process. The P wave is normally an upward deflection. We have seen that the direction of an electrical deflection is an index of the path which the excitation process is taking. If the S.A. node is artificially stimulated during diastole and a new impulse set up there, a normal P wave is obtained, because the *forced excitation* process is taking the normal route. If the impulse is set up from any other point on the auricle, the P wave is abnormal in character—flattened or inverted —showing that an unusual path has now been taken by the excitation process.

3. If the S.A. node is extirpated, the P wave disappears or becomes inverted (Fig. 68), showing that a new site of impulse formation has been set

up. It is worthy of note that the new "pacemaker" usually proves to be the auriculo-ventricular node.

4. Cooling the S.A. node within physiological limits slows, and warming it quickens, the whole heart. These effects cannot be produced from any other part of the auricle.

Spread in the Auricle.—The impulse spreads out uniformly from the S.A. node over the walls of both auricles as a ripple spreads out over a pond into which a stone has been dropped, or as the spread of fluid poured on to a flat surface. It spreads through the auricular muscle to reach the muscular sleeves surrounding the openings of the great veins, and the auriculo-ventricular node which lies in the posterior part of the right auricle. There is no evidence that any special connecting band exists between the S.A. and A.V. nodes.

Bundle of His.—Experimental evidence proves that the bundle of His is the sole connecting strand between the auricles and ventricles. If the bundle of His is compressed, a proportion of the auricular impulses may fail to reach the ventricles, the rate of which may be only half that of the auricles. If the bundle is completely divided in animals or destroyed by disease in man, the auricles and ventricles are completely "dissociated," and beat quite independently one of the other. The auricles beat at their usual rate in response to impulses generated in the S.A. node, while the ventricles beat much more slowly—thirty to forty times per minute—in response to a new rhythm centre in their own substance, probably in the lower part of the bundle (cf. pp. 239 and 269).

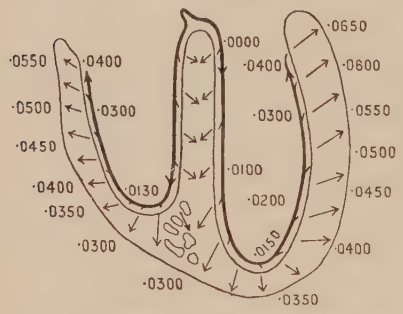

Fig. 69.—Diagram to illustrate the Time Relations of the Spread of the Excitation Process in the Ventricles. The figures represent time in seconds; zero time, ·0000, represents the arrival of the excitation process at the top of the interventricular septum.—Lewis.

Spread in the Ventricles.—The impulse spreads down both branches of the bundle of His to reach the right and left ventricles separately. If one branch of the bundle is divided (say the right branch), the left ventricle receives its impulse normally, but the impulse only reaches the affected right ventricle after some delay, because it must spread across from the normally stimulated left side (cf. p. 236). Fig. 69 illustrates the time relations of the activation of the various parts of the ventricles. The septum is excited first, then the apex of both ventricles, and lastly the base of the heart. It takes the impulse 0·013 second to pass from the bundle of His to the apex, and 0·040 second to arrive at the endo cardial surface of the base of the left ventricle. The impulse is carried from apex to base by the special Purkinje fibres, and injury to the endocardial surface of the heart beneath which this tissue lies delays the propagation of the impulse. From each point on the endocardium, the excitation process affects the corresponding part of the pericardial surface. An extensive injury to the pericardial aspect of the ventricle does not interfere with the conduction of the impulse. The last part of the heart to become excited is the pericardial surface of the base

of the ventricle, 0·055 second in the case of the right base, and 0·065 second for the left base. It must be noted that the whole of both ventricles is invaded by the excitation wave in well *under 0·1 second* (Lewis).

The figures quoted are based on results which have been obtained in the dog by the electrical method of timing the arrival of the impulse at various points on the ventricle.

Rate of Conduction.—The rate of conduction in the auricle is 1000 mm. per second, in the A.V. node 200 mm. per second, in the bundle of His and Purkinje fibres 4000 mm. per second, and in the ventricle 400 mm. per second.

The Human Electro-Cardiogram.—The electrical variations produced by the heart during contraction are distributed through the body, and can be led off from the moist skin surface of the arms and legs, and recorded by means of a sensitive galvanometer. In the Einthoven string galvanometer there is an exceedingly fine silvered glass fibre which is suspended in a box and placed vertically between the poles of a powerful electro-magnet. When a current passes through the fibre minute oscillations occur. The shadow of the oscillating fibre is magnified, projected on a moving photographic plate, and a permanent record is thus obtained. The tension of the fibre affects

Fig. 70.—Normal Electro-Cardiogram. Time record above in one-fifth seconds.—Price.

its sensibility, and it is customary so to adjust the tension that when a difference of potential of 1 millivolt exists between the two ends of the fibre a deflection of 1 cm. on the photographic plate is obtained.

Three leads are employed: Lead I., from right arm and left arm; Lead II., from right arm and left leg; Lead III., from left arm and left leg. Figs. 70, 71 show the normal curves obtained. A proper understanding of the significance of the electro-cardiogram is of great value, because "it forms a graphic record of the functional changes in the heart muscle" (Goodall).

P.—The first upward deflection P has a rounded or pointed summit, and its duration is 0·1 second.[1] It represents the passage of the excitation process over the auricle; the A.V. node is reached at about the *summit* of P. The extent of the P wave is a reliable guide to the functional activity of the auricular muscle. In *mitral stenosis* the left auricle is hypertrophied, and correspondingly the P wave is prominent, or bifurcate. Bifurcation of the wave may be due in this case to the abnormal relationship in the mass of the two auricles. In *auricular fibrillation* the P wave is replaced by a series of fine irregular oscillations, corresponding to the rapid irregular excitation of the auricles. If the cardiac impulse arises in an abnormal focus and spreads in other than the usual direction, the P wave is altered or even inverted,

[1] "P" is referred to as the "auricular complex."

becoming a downward deflection (Fig. 82). The P wave may be prolonged if the proper spread of the excitation process is hampered by a hypertrophied or damaged muscle.

QRST.[1]—Following P is a brief iso-electric period, after which is seen a small, often inconspicuous, downward deflection Q, a prominent upward deflection R, and a definite downward deflection S. QRS represent the *invasion* of the ventricular wall by the excitation process. The time interval from the beginning of P to the commencement of R, or P–R interval, is referred to as the conduction time of the bundle of His. The *true* conduction time is the interval from the top of P (where the A.V. node is excited) to the beginning of Q (where the invasion of the ventricles commences). It is easier, however, to measure the P–R interval (the Q wave is inconstant and of small size), and undoubtedly it is mainly taken up in the passage of the impulse along the bundle and its branches. The P–R interval in health varies between 0·13 and 0·16 second, the extreme limit of the normal being 0·21 second. If it exceeds 0·2 second, it is definite evidence of delayed conductivity in the bundle of His. If the P–R interval is shorter than normal, the impulse has probably arisen in the A.V. node and has excited auricle and ventricle more or less simultaneously (cf. Fig. 81). The whole QRS complex usually lasts less than 0·08 second and should not exceed 0·1 second. (It will be remembered that the invasion of the ventricles is probably complete in 0·065 second.) Q represents activity in the region of the interventricular *septum*, and is absent in animals not possessed of a septum (*e.g.* amphibians and reptiles). In Lead II., which is the one most usually studied, R represents mainly activity in the *right* ventricle, while S is chiefly related to the *left* ventricle (Fig. 71). QRS just precedes the mechanical contraction of the ventricles and the first heart sound (Fig. 78). If one or other branch of the bundle of His is damaged so that the excitation process is unable to spread normally, the QRS is prolonged and may exceed in duration 0·1 second (Fig. 72). It is followed by an iso-electric period of *possession* during which all parts of the ventricle are equally excited. This is succeeded by a broad upward deflection T. The average duration of the whole QRST complex is 0·43 second. The end of T either just precedes or just follows the second heart sound.

The mode of production of the T wave is not known for certain. In the case of the simple strip of muscle, the second deflection of the diphasic variation represented persistence of the excitation process at the distal end of the muscle after it had retreated or passed off completely from the proximal end. The excitation process in the ventricle spreads from apex to base. Arguing from analogy, one may say the excitation process passes off earlier at the apex, and remains longer or more extensively at the base. T thus represents the *retreat* of the wave from the apex and its persistence at the base. Why the T wave should be an upward deflection and not in the reverse direction to the main initial wave is not yet satisfactorily cleared up.

The T wave is readily influenced by many factors. It is altered by stimulation of the vagus or the sympathetic ; by many poisons ; it is early inverted by toxic doses of *digitalis*. The digitalis effect may persist for 5 to 22 days after the drug has been stopped (Goodall). T is sometimes inverted in Lead III. for no very obvious reason.

In young healthy adults the T wave is very conspicuous, has an amplitude

[1] " QRST " is referred to as the " ventricular complex."

of 2·5 mm. to 3·9 mm. in Leads I. and II., and a duration of 0·27 second. In old age the T wave is flattened and less conspicuous—in an old man of eighty-four the amplitude was 1 mm. in Lead I. and 2 mm. in Lead II., and the duration was 0·2 second (Strickland-Goodall). The most marked effect of exercise in healthy young adults on the electrical record, apart from the shortening of the diastolic pause owing to the acceleration of the heart, is to increase the amplitude of the T wave.

Goodall, from an analysis of numerous records, found that any abnor-

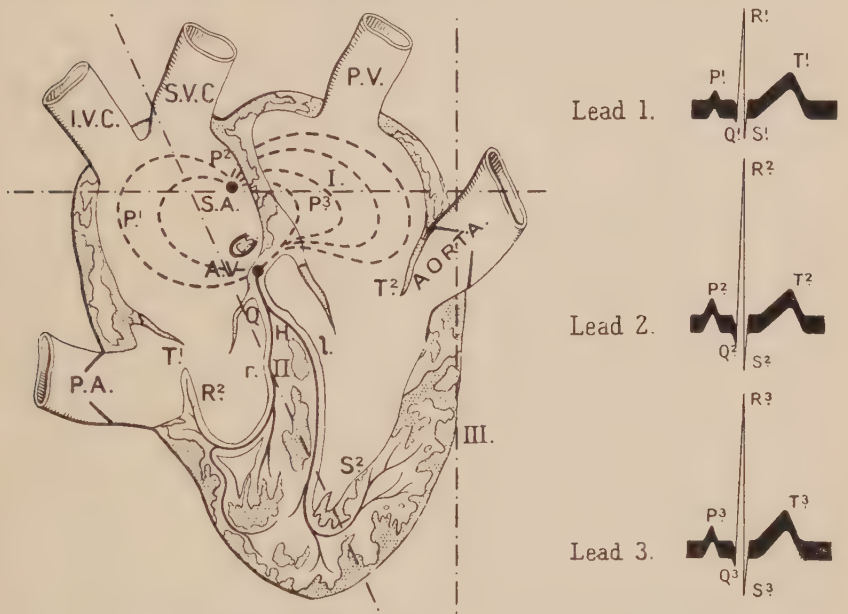

FIG. 71.—Diagrammatic Representation of Heart, showing Probable Relationships of Electro-Cardiographic Waves to different parts of Myocardium. The electro-cardiographic curves on the right represent "normals" for young healthy men under 30 years of age. They were constructed from mean measurements obtained from a number of Middlesex Hospital students.

S.A.=Sino-auricular node; A.V.=Auriculo-ventricular node; C.S.=Coronary sinus; H.=Main bundle of His; r., l.=Right and left branches; P.A., P.V.=Pulmonary artery and vein; Broken lines I., II., III. represent the three leads which are used; P^1, P^2, P^3, etc., on heart refer to corresponding electro-cardiographic waves.—J. STRICKLAND-GOODALL.

mality of the T wave in either form, direction, or reaction to exercise in Leads I. and II. is evidence of serious cardiac damage, is of grave significance, and is particularly liable to be associated with sudden and unexpected death.

It is concluded that the T wave is related to the functional state at the base of the ventricles. When this region of the heart is damaged (*e.g.* in aortic regurgitation, gummatous, or other forms of myocarditis), abnormalities of the T wave occur.

To understand the part played by each ventricle in contributing to the QRS complex it is necessary to study the electro-cardiographic records

obtained after division of one or other branch of the bundle of His in animals, or in analogous conditions resulting from disease in the human subject. If the right division is destroyed, the left ventricle receives the excitation process in a normal manner. No impulse reaches the right ventricle from the ordinary channels, and it must wait for the excitation wave to spread to it from the substance of the left ventricle. In the electrical records, the *initial* ventricular variation must represent in the above example *left* ventricular events ; the later variations will be modified by the delayed onset of right ventricular activity. To such a curve, which in its initial phases is predominantly left

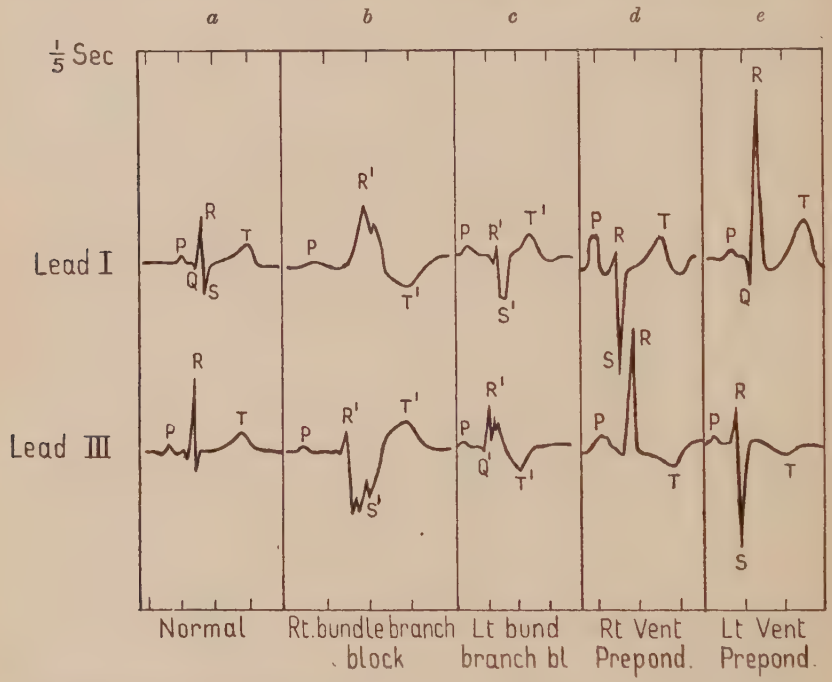

Fig. 72.—Electro-Cardiographic Records (Leads I. III.) in various conditions (Diagrammatic). (See text.)

ventricular in origin, the term *lævo-cardiogram* is applied. By dividing the left division of the bundle, a *dextro-cardiogram* is obtained, throwing light on the contribution of the right ventricle to the electro-cardiographic record. The curves in man and animals are remarkably similar, and in Fig. 72 *b*, *c* are shown tracings illustrating the two conditions.

Human Lævo-Cardiogram (Division of Right Branch of Bundle).— In Lead I. : an inconstant Q′ wave ; a tall broad R′ which is often notched. In Lead III. : a small R′ wave ; a broad extensive dip S′ (Fig. 72 *b*).

The great amplitude of the main initial wave should be noticed. The T′ wave in each lead is in the opposite direction to the main initial wave, *i.e.* a deep, round, downward deflection in Lead I., and an upward deflection

in Lead III. (In Lead II. R′ and S′ are intermediate in size, and both are of moderate extent.)

It follows from the above findings that in Lead I. R is a left-sided event, and in Lead III. S is a left-sided event. The abnormal Q′R′S′ always exceeds the normal limits of 0·1 second and averages 0·14 second. This is readily understood when it is recalled that the right ventricle only receives the excitation process after considerable delay at second-hand, so to speak, from the left ventricle.

Human Dextro-Cardiogram (Division of Left Branch of Bundle).—In Lead I.: a small R′; a deep broad S′. In Lead III.: a small Q′; a tall, broad, notched R′; a negligible S′ (Fig. 72 *c*).

T′ is again in the opposite direction to the main initial deflection, and so is upright in Lead I. and inverted in Lead III. Lead II. is again not characteristic.

Clearly S′ in Lead I. and R′ in Lead III. represent right ventricular events.

On the whole, Lead II. is most nearly related to Lead III., and so, as stated above (p. 234), R in Lead II. is chiefly right ventricular and S is chiefly left ventricular in origin.

In animals a normal electro-cardiogram can first be obtained. The left and then the right division of the bundle are clamped, and dextro- and lævo-cardiograms respectively obtained. If such curves be superimposed one over the other, and the algebraic sum of the initial deviations calculated in each lead, the curve thus charted is identical in shape and amplitude with the initial deflections of the normal electro-cardiogram in all leads. In other words, the normal QRS complex is the sum of individual electrical quotas contributed by both ventricles.

Preponderance of a Ventricle.—If one ventricle is showing excessive functional activity relative to its fellow, we would expect its distinctive contribution to the electro-cardiogram to be recognizable. In preponderance of the *left* ventricle, the curve should tend to resemble the lævo-cardiogram; and similarly, in preponderance of the right ventricle, the dextro-cardiogram should impress itself excessively on the tracing. The results found are as would be predicted (cf. Fig. 72 *e* and *b*, *d*, and *c*).

In preponderance of the left ventricle: (Q and) R in Lead I. and S in Lead III. are exaggerated (cf. lævo-cardiogram, Fig. 72 *e*).

In preponderance of the right ventricle: S in Lead I. and (Q and) R in Lead III. are exaggerated (cf. dextro-cardiogram, Fig. 72 *d*).

The amplitude of the main initial deflections is typically not so great as in the case of the bundle lesions. The QRS complex is slightly prolonged, but not to the same extent as in damage to branches of the bundle. The greater thickness of the muscle wall of the preponderant hypertrophied ventricle accounts for the slight delay in completing the invasion of the ventricles and the consequent widening of the QRS complex.

Ventricular Extra-Systoles.—If one or a series of heart beats arise for some reason in a focus in one ventricle, one would expect these "ectopic" beats or ventricular extra-systoles to leave an impress on the electrical record. The whole problem is discussed fully on p. 270, but it is obvious that if the impulse arises in the left ventricle, that ventricle responds first, and the right ventricle is excited later. The initial phases of the ventri-

cular complex should resemble the lævo-cardiogram. Similarly, in right ventricular extra-systoles the dextro-cardiogram modifies the initial electrical variations. We thus find :

Left ventricular extra-systole :

Lead I. : usually big R′ wave. T′ wave inverted.

Lead III. : big S′ wave. T′ upright.

Right ventricular extra-systole (Fig. 83) :

Lead I. : sometimes big S′ wave. T′ upright.

Lead III. : big R′ wave. T′ wave inverted.

The electro-cardiograms in the case of ectopic ventricular beats may not be easy to interpret.

Heart Block.—By heart block is meant a condition in which there is defective conduction in some part of the heart.

The following varieties of heart block may be recognized :

1. Sino-Auricular Heart Block.—This is a rare condition in which a

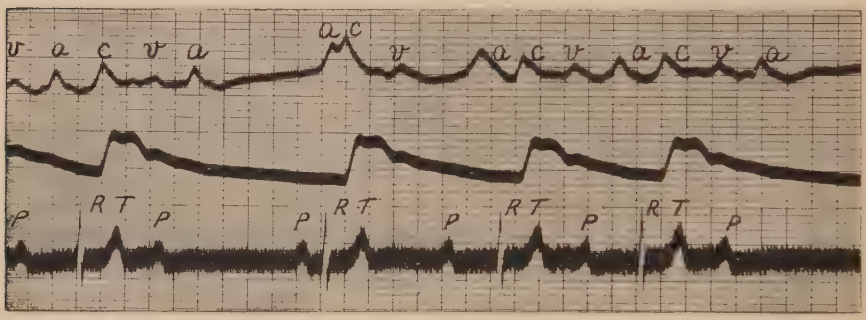

Fig. 73.—Simultaneous Venous, Radial, and Electro-Cardiographic Curves from Patient, showing " Dropped " Beats.

The second P wave in the electro-cardiograph curve is not followed by a ventricular complex ; similarly, the second *a* wave is not followed by *c* and *c* waves ; nor is there any corresponding pulsation at the wrist. Following this dropped beat (long pause in the pulse tracing) the P-R and *a-c* intervals are short ; in the succeeding cycles they lengthen. Notice that the *increase of the second* P-R (*and a-c*) *interval over the first is greater than the increase of the third over the second* ; this shortens the inter-ventricular period directly preceding the next dropped beat, *i.e.* the ventricle quickens to the point of disturbance. Following the next dropped beat the events are repeated. Time (vertical lines) in fifths of a second.—Lewis.

whole heart beat is lost at varying intervals. During this pause there is neither auricular nor ventricular contraction, nor does any electrical variation occur. After an interval which is usually less than two complete cycles, the heart resumes its normal action. Occasionally every other beat is suppressed completely, and a profound slowing of the whole heart to about 30 per minute is noted. The condition is at once unmasked by exercise, when the missing beats reappear, and the heart suddenly doubles its rate. It then further accelerates gradually like a normal heart.

S.A. heart block may be produced by vagal stimulation, and is relieved by paralysis of the vagus with atropine, or by exercise when vagus tone is diminished. The clinical condition is perhaps due to heightened vagus tone acting on a susceptible S.A. node. Block is produced *within* the substance of the node, and the impulse never gets out to activate the rest of the heart.

2. Main Bundle Block.—If the bundle of His is compressed, it becomes a region of impaired conduction, and changes occur in the following order :

(1) Delayed conduction (P–R interval exceeds 0·2 second).

(2) Failure of occasional and then of more impulses to reach the ventricle (see Fig. 73).

(3) The ventricle responds to every second, third, or fourth impulse from the sinus, as shown by the establishment of ratios like 2 : 1, 3 : 1, 4 : 1 between the auricular and ventricular beats (Fig. 74).

The above conditions are called *partial* heart block.

(4) *Complete* heart block : none of the sinus impulses reach the ventricle. The beats of auricle and ventricle are completely dissociated, and bear no relation whatever to one another. The ventricle now beats with an independent rhythm.

When 2 : 1 block is established, the electro-cardiogram shows regularly spaced P waves, which are twice as numerous as the ventricular complexes. When complete block is present, the independent ventricular beats arise from the most rhythmic part of that chamber. This is the region of the bundle just below the site of the block. The excitation process, therefore, reaches the two ventricles along the normal channel of the two branches of the bundle. The ventricular complex is normal in character, but is in no way related in time to the auricular wave.

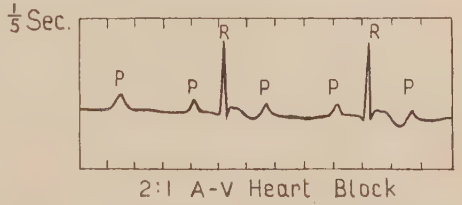

Fig. 74.—Note that Auricular Complexes (P) are twice as numerous as Ventricular Complexes (R).

3. Branch Bundle Block (see p. 236).

Effects of Heart Block.—While the heart block is partial, the ventricle is beating slowly but in response to auricular impulses. The circulation is fairly effectively carried out at rest, the diminished rate being compensated for by the larger output per beat. Exercise is greatly limited because the necessary acceleration of the heart to cope with the greater venous return cannot take place. If the heart block becomes complete *suddenly*, the ventricle may stop beating temporarily. (The same result is obtained when a ligature is tied between the auricle and ventricle of the frog (" Stannius ligature ").) Some little time elapses before it can accustom itself to the new conditions, and so the ventricle is quiescent until it begins beating at its own rate.

A certain minimal rate of the heart is necessary to maintain an adequate circulation. If the ventricle is profoundly slowed or brought to a standstill, nervous symptoms occur which are due to oxygen lack. (Identical symptoms result from compression of the carotid arteries.)

1. For the first few seconds nothing abnormal is felt.

2. If asystole lasts 5 seconds, momentary unconsciousness may occur. After 15 seconds, twitchings, convulsions, sighing or deep breathing, and cyanosis are present.

3. After 90 to 120 seconds, death results. Heart block associated with fainting attacks as just described constitutes the *Stokes-Adams* syndrome.

Properties of Heart Muscle.—1. Excitability and Contractility.—Heart muscle is *excitable, i.e.* it responds to external stimuli by *contracting.* The "all-or-none" law discussed when dealing with nerve applies equally well to the heart. If the stimulus is adequate, the heart responds to the best of its ability. From the functional point of view heart muscle behaves as a single unit, so that an adequate stimulus normally makes the whole heart contract. The actual *force* of the contraction varies with the state of the muscle, and depends on the following factors :

i. *Diastolic* pause. If the heart has not fully recovered from the effects of a previous contraction (short diastole), or if it is suffering from the injurious action of poisons or drugs, the force is diminished.

ii. *Initial length* of fibres. Up to a point, the greater the *initial length* of the heart muscle fibres at the onset of systole, the more forcible is the contraction. If the heart is underfilled (*e.g.* after hæmorrhage, in obstruction to the mitral orifice), the beat is feeble. If the venous return is large and the diastolic filling of the heart is great (*e.g.* muscular exercise), a powerful beat is obtained. Should the heart be excessively filled, the fibres are overstretched and are unable to contract effectively; the heart does not then empty itself completely at each beat.

iii. *Nutrition* and *Oxygen,* supply of heart (p. 242).

The true *latent period* of heart muscle, *i.e.* the time period elapsing between the artificial stimulus and the onset of physico-chemical changes in the underlying tissue, is very brief, about 0·002 second. Mechanical shortening of the fibres can be recorded about 0·02 second later. It should be remembered that the ventricular muscle, because of its great mass, forms the great driving power of the heart.

2. Refractory Period.—(*a*) Throughout the period of contraction, heart muscle is "*absolutely refractory*" and does not respond at all to external stimuli. Summation effects are impossible, because one contraction must be completed and recovered from before a fresh one can begin.

(*b*) Shortly after the contraction is over, the muscle is "*relatively refractory.*"[1] Minimal stimuli fail to produce a response, but very strong stimuli are effective. The force of contraction during this period is also subnormal.

(*c*) Recovery rapidly occurs, and the muscle may perhaps pass through a "*supranormal phase*" during which excitability and contractility are both increased before there is a return to the normal state.

The refractory period is longest in the A.V. node, intermediate in the ventricle, and shortest in the auricle. Certain drugs—like digitalis and quinidine—prolong the absolute refractory period; stimulation of the vagus shortens the duration of systole, and so *diminishes* the refractory period.

During contraction it is believed there is a movement of ions in relation to an ensheathing colloid membrane, so that the active region becomes galvanometrically "negative." During relaxation the ions return to their normal position, and excitability is regained (cf. p. 15).

3. Conductivity is a property of all heart muscle, but is especially developed in the bundle of His and its branches (the "Purkinje tissue").

[1] The absolute refractory period of auricular muscle has been carefully studied. At heart rates up to 100 per minute it is 0·2 second (p. 272).

Conduction in Purkinje tissue is at the rate of 4 metres per second, in the auricular wall 1 metre per second, and in the ventricular wall 0·4 metre per second. In the A.V. node conduction is very slow—about 0·2 metre per second. It will be remembered that nervous tissue in mammals conducts at the rate of 120 metres per second. The excitation process is normally transmitted from one point on the heart to the adjacent one with no diminution of intensity, as in nerve. When the Purkinje tissue is damaged, it conducts more slowly and with diminished intensity like nerve tissue poisoned by alcohol. Conductivity is a very stable property, and when it is depressed the fibres are probably verging on death. Drugs which depress conductivity also diminish excitability, and in larger doses may kill the fibres.

Rhythmicity.—The heart has the power of initiating its impulse, apparently without recourse to external agencies. Normally this function is carried out by the S.A. node. It is suggested that, during the recovery stage, excitability returns to such a degree in the S.A. node that an impulse is spontaneously generated.

Law of Cardiac Muscle.—The musculature of the heart may be divided into four classes: (i) Fine fibres at the nodes; broader fibres of (ii) ventricle; then (iii) auricle; and lastly, the broadest fibres of (iv) the Purkinje tissue. The fundamental properties of muscle under physiological conditions are found to vary quantitatively in the four types of cardiac fibre.

Fibre.	Fibre Size.	Glycogen Content.	Rate of Conduction.	Length of Systole (Refractory Period).	Rhythmicity.
Nodal . .	1	1	0·2 m.p. sec.	4	4 High.
Ventricular .	2	2	0·4 „	3	3 Low.
Auricular .	3	3	1·0 „	2	(?) 2
Purkinje .	4	4	4·0 „	(?) 1	(?) 1

(Lewis.)

The size of fibre, glycogen content, and rate of conduction increase from nodal to Purkinje tissue. The length of systole, duration of the refractory period, and rhythmicity increase in the reverse order (cf. p. 14).

Tonus.—The modern conception of tone in smooth muscle is that of maintaining constant internal pressure in spite of varying size of content. Presumably during diastole the heart fibres must elongate in order to enlarge the cavity and thus enable more blood to be accommodated. The greater the venous return the greater must be this active diastolic lengthening of the muscle fibres. This may be called physiological dilatation of the heart. Clinically the term "dilated heart" is used in a very vague manner, and refers to a heart which is believed not to empty itself completely with each systole. The output is lessened, and some blood may be left behind after each contraction.

Nutrition of the Heart.—This may be studied by perfusing the isolated

heart. The heart is removed from the body, the vessels springing from the aortic arch are ligated, and a cannula is inserted into the descending aorta pointing towards the heart. Fluid of varying composition under different pressure is forced into the cannula, closes the semilunar valves, perfuses the coronary arteries, and thus reaches the heart muscle. The fluid returns to the right auricle *via* the coronary sinus. The heart is attached to a recording lever and is soon found to contract rhythmically.

1. Temperature.—Cooling the perfusing fluid slows the heart and may finally stop it. Warming the fluid quickens the heart. The effect is probably to alter the rate of metabolic activity in the S.A. node.

2. Pressure.—If the pressure of the perfusion fluid is lowered, the force of contraction is diminished (cf. p. 243).

3. Oxygen Supply.—If this is inadequate, the beat becomes feeble and irregular.

4. Constituents of the Perfusing Fluid.—The inorganic constituents are more important than the organic. For the mammalian heart, fluid with the following salt concentration is best:

NaCl, 0·9 grm. $CaCl_2$, 0·024 grm. KCl, 0·042 grm. $NaHCO_3$, 0·01 to 0·03 grm. Distilled water, 100 c.cm.

The part played by each constituent is as follows:

Na.—(i) The NaCl gives the fluid its proper osmotic pressure so as to be in equilibrium with the tissues.

(ii) Na plays a special rôle in maintaining and originating the heart beat. Isotonic cane sugar solution does not produce rhythmic activity of the heart until Na is added.

Ca. If Ca ions are added to the perfusing fluid, the force of the heart is increased. If Ca is present in excess, the heart contracts well, but relaxes progressively less; the beats become steadily smaller in extent, and finally the heart stops in a condition of extreme contraction—*calcium rigor*.

K.—Excess K causes increasing relaxation of the heart, and finally brings about arrest in complete diastole.

H Ion Concentration.—$NaHCO_3$ is added to make the fluid slightly alkaline.

i. Increased H ion concentration causes relaxation of the heart and feebleness of the beat.

ii. Excessive alkalinity produces the reverse effect. Excessive artificial respiration in an intact animal results in washing out of CO_2 from the blood and alkalæmia. The heart contracts forcibly but does not relax during diastole to receive the venous return, and so the output and blood pressure fall (cf. p. 300).

Glucose.—0·1 per cent. glucose is helpful in providing the source of energy for the cardiac contraction. The ingestion of large quantities of glucose is recommended in the treatment of cardiac failure.

The contraction of cardiac muscle (like that of skeletal muscle) probably depends on the liberation of lactic acid from glycogen. The heart fatigues when a lactic acid maximum only one-third as high as that of skeletal muscle is reached, *i.e.* about 0·1 per cent. (cf. p. 354).

Coronary Circulation.[1] (i) *Nerve Supply.* The coronary vessels receive a rich innervation from both the vagus and the sympathetic, as shown

[1] Anrep and Segall, *Heart*, 1926, vol. xiii. p. 239.

by degeneration experiments. The vagus is said to convey *constrictor* fibres to the coronary arteries. Section of the vagi increases, and stimulation of the peripheral end of the vagus diminishes the coronary flow; in the latter case the same result is obtained even if the heart is artificially maintained at its previous rate by means of electrical stimulation. Stimulation of the sympathetic *dilates* the coronary arteries; according to Anrep and Segall cerebral anæmia and asphyxia produce coronary dilatation in part by stimulation of the sympathetic supply to the coronary vessels.

(ii) (α) *Anoxæmia* greatly increases the coronary flow; a fall in the oxygen saturation of the arterial blood to 80 per cent. has little effect, but a fall to 50 per cent. may increase the flow 4- to 5-fold. (β) *Excess* CO_2 has a much smaller effect. A change in the CO_2 content of the inspired air from 3 to 7 per cent. (which raised the H ion concentration of the blood from *p*H 7·7 to *p*H 7·35) only increased the coronary flow by 50 per cent. (γ) *Adrenaline* dilates the coronary arteries in most species: isolated strips from the larger branches of the coronaries of man are constricted by adrenaline, but strips from the smaller branches are dilated. (δ) *Histamine*, which may possibly be liberated in active tissues (p. 292), has varying effects in different species: the coronaries of the cat are dilated, of the dog and ox—constricted.

(iii) *Influence of Arterial Blood Pressure.*—The mean aortic blood pressure [1] is probably the main factor which controls the coronary circulation. Thus in the denervated heart-lung preparation (dog) (p. 262) an increase in mean blood pressure from 50 to 130 mm. Hg may increase the coronary flow from 20 to 250 c.cm. per minute. A *low blood pressure* from any cause thus results in an impaired blood supply through the coronaries, and defective nutrition of the heart, which further depresses the state of the circulation.

(iv) *Influence of Cardiac Output.*—In the denervated heart-lung preparation, variations in the cardiac output have negligible effects on the coronary flow if the mean blood pressure is kept constant. If the nerve supply of the heart is intact it is found that the *coronary flow increases as the cardiac output increases.* Anrep attributes this to *reflex inhibition* of the vaso-constrictor fibres to the coronary arteries which are carried in the vagus nerves.

(v) *Coronary Flow during the Various Phases of the Cardiac Cycle.*[2]—The coronary arteries fill during the *early part of ventricular systole and during diastole.* The coronary inflow begins to rise as soon as ventricular systole ends and quickly attains its maximum, at which level it persists until the end of the phase of isometric ventricular contraction (p. 247). During the ejection phase of ventricular systole the coronary flow is cut down to a minimum in spite of the raised intra-aortic pressure; this is attributed to compression of the intramuscular branches of the coronary vessels. The *outflow* from the coronary sinus is, however, greatest during the ejection phase, and is also increased to a less extent during auricular systole.

(vi) *Coronary Flow in Exercise.*—The maximum output of the heart per minute in exercise is about 40 litres. Let us assume the mean blood pressure to be 100 mm. Hg. The *work* of the left ventricle is consequently $\frac{40 \times 100}{760}$ litre-atmospheres $= 530 \times 110^7$ ergs $= 28$ calories.[3] If the

[1] By "mean blood pressure" is meant the mean of systolic and diastolic pressure.
[2] Anrep and others, *Heart*, 1927, vol. xiv. p. 111.
[3] The small calorie is here referred to.

mechanical efficiency[1] of the heart is 20 per cent., the total energy liberated is $128 \times 5 = 640$ calories per minute. If the work of the right ventricle is one-fourth that of the left (owing to the low pulmonary pressure), the total energy output of the heart is $640 + 160 = 800$ calories per minute. 160 c.cm. O_2 are needed to liberate this energy (1 c.cm. $O_2 = 5$ calories). If 12 c.cm. O_2 are obtained from each 100 c.cm. of coronary blood, the flow through the coronary arteries must be *1·4 litres per minute* (which is two to three times the volume of the heart) (Hill). This immense coronary flow may be attributed in the light of the results discussed above to (i) great reduction in the oxygen content of the blood ; (ii) rise of CO_2 tension and of H ion concentration of blood ; (iii) secretion of adrenaline ; (iv) reflex inhibition of the vagal vaso-constrictor fibres.

(vii) *Results of Coronary Occlusion.*[2]—Experimentally[3] it is found that if both main branches of the left coronary artery are tied, death usually results immediately from ventricular fibrillation (p. 278). If the circumflex or anterior descending branch alone is ligated, no serious results may be noted. Thus the anterior descending branch was tied in 11 dogs : 1 died immediately, 1 died on the seventeenth day from heart failure, and 7 survived until deliberately sacrificed. If the right coronary artery is ligated, about half the experimental animals may survive for longer or shorter periods. Clinically[4] coronary occlusion may prove fatal instantaneously or within a few minutes, hours, or days, or death may occur later from heart failure or good recovery may take place. The condition is characterized by *pain* which is similar to that of angina pectoris, but is more severe and prolonged, persisting for hours or days, and being relatively unaffected by morphia. There is little doubt (cf. p. 137) that angina is frequently the result of coronary occlusion. The " referred pain " in this condition has a very wide distribution : it is experienced not only in the chest, neck, and arms, but also in the interscapular area and in the epigastrium, and may be accompanied by tenderness and rigidity of the abdominal wall, nausea, and vomiting. There are marked signs of *shock* : ashen grey hue, sweating, and a very feeble pulse. The *blood pressure* falls markedly, sometimes to an extent which interferes with the secretion of urine (p. 463). The usual signs of heart failure may develop.

[1] Cf. p. 278.

[2] The detailed distribution of the coronary arteries is described by Gross (*Blood Supply of Heart*, 1921, New York); the anterior descending branch of the left coronary is particularly important because it is occluded more often than all the other branches added together. This branch supplies portions of *both* ventricles, *i.e.* the apex of the left ventricle, the left anterior third of the right ventricle, and part of the interventricular septum. There is a rich anastomosis between the branches of the same artery and between the right and left coronaries in their capillary and precapillary distribution. The vascular needs of heart muscle are so enormous, however, that if a sufficiently large branch is blocked death of the corresponding region of the heart (infarction) may take place. If a coronary vessel is slowly narrowed an adequate collateral circulation is gradually established so that the vessel may finally be completely closed without harm. According to Gross, anastomoses throughout the coronary circulation become more effective and more extensive with advancing years, so that other factors being equal the heart of a man at 60 is better prepared to withstand the effects of coronary occlusion than the heart of a man at 20. The results of coronary occlusion therefore depend on the size and location of the vessel, the rate of formation of the thrombus, the age, and the state of the general circulation.

[3] Smith, *Arch. Int. Med.*, 1918, vol. xxii., p. 8 ; 1920, vol. xxv. p. 673 ; 1923, vol. xxxii. p. 497 (Experimental Occlusions).

[4] Hamman, *Johns Hopkins Hosp. Bull.*, 1926, vol. xxxviii. p. 273 (full bibliog.).

Movements of the Heart.—The heart is enclosed within the pericardium, which is fixed above to the great vessels and below to the central tendon of the diaphragm. The fibres of the heart are arranged in a complex spiral manner.

1. During systole, all the diameters of the heart are decreased and the position of the organ alters. The base and auriculo-ventricular ring descend; the apex of the heart is rotated anteriorly and moves down slightly. It is thus brought into closer apposition with the chest wall, and this impact mainly accounts for the *apex beat*, which is the shock felt in the fifth intercostal space.

2. The entire heart moves downwards during inspiration, and the apex is rotated clockwise. The shadow of the heart, as seen during X-ray examination, lengthens and becomes narrower.

3. The position of the heart alters with that of the body. It is displaced to the left and pressed more firmly against the chest wall when lying in the left lateral position. Anything which pushes the diaphragm up—*e.g.* assuming the sitting or the prone position, flatulence, etc., causes the heart to lie more horizontally.

REFERENCES

Lewis.—*Mechanism and Graphic Registration of Heart Beat*, 3rd Edn., London, 1925; *Clinical Electro-Cardiography.*

Anrep.—*Physiol. Rev.* 1925, vol. vi. p. 596 (Coronary Circulation).

II

Pressure changes in the heart and blood vessels—Ventricle—Auricle—Jugular vein—Aorta—Velocity of pulse-wave—Central arterial pulse—Radial pulse—Heart sounds—Reduplicated sounds.

Rate of heart—Vagus—Effects of stimulation—Mode of action—Sympathetic—Regulation of heart-rate—Higher centres, respiration, reflexly—Depressor nerve—Auricular reflex—Anoxæmia, CO_2, temperature, intracranial pressure.

Output of heart—Methods—Douglas and Haldane—Hill—Ethyl iodide—Heart-lung preparation—Venous return—Law of heart—Relation of output to metabolism, gravity, external temperature, blood pressure, heart-rate—Paroxysmal tachycardia—Heart block—Mitral incompetence—Aortic regurgitation.

New rhythm centres—Auricular and ventricular extra-systoles—Response of auricle to rapid stimulation—Ring experiment—Circus movement—Auricular flutter—Auricular fibrillation—Digitalis and quinidine—Ventricular fibrillation.

Pressure Changes in the Heart and Blood Vessels.—In the most accurate work, optical methods are employed. Wiggers uses a vertical glass tube surmounted by a tense rubber membrane upon which a small mirror is fastened. This cannula is filled with anti-coagulant fluid and introduced directly into the chamber of the heart to be examined. Pressure changes in the cavity produce oscillations of the mirror which reflects a beam of light on to a moving photographic plate. The volume changes in the heart during the cardiac cycle under varying conditions can be determined by means of Henderson's cardiometer. A glass vessel resembling a thistle funnel is placed over the ventricles and is fitted round the auriculo-ventricular groove. It is connected with a piston recorder which writes on a moving smoked surface.

Ventricle.—1. At the onset of ventricular *systole*, the pressure in the auricles and ventricles is approximately the same. The auriculo-ventricular

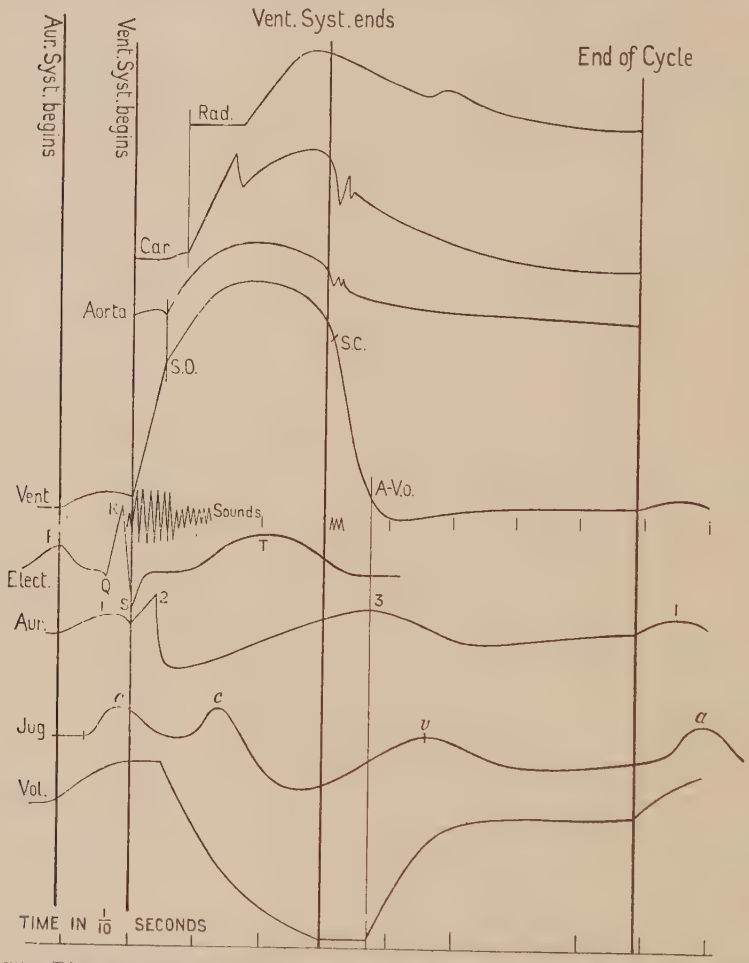

FIG. 75.—Diagram of Pressure, Volume, and Electrical Changes in Heart and Blood Vessels during the Cardiac Cycle.—Modified from LEWIS and WIGGERS.

Vol. = Volume curve of left ventricle; Jug. = Jugular venous pulse; Aur. = Intra-auricular pressure; Vent. = Intraventricular pressure; Elect. = Electro-cardiogram; Aorta = Intra-aortic pressure tracing; Car. and Rad. = Carotid and radial pulse; S.O., S.C. = Opening and closing of semilunar valves; A-V.o. = Opening of auriculo-ventricular valves. (See text.) The duration of the cardiac cycle is shown as 0·9 second, corresponding to a heart-rate of 67 per min. If the rate is 72, the duration of the cycle is 0·8 second; the period of diastasis is then shorter.

valves are floating into apposition. As the ventricular muscle contracts, the pressure rises steeply. The A.V. valves are shut and bulge slightly in a dome-shaped manner into the cavity of the auricles, causing a sudden rise of

intra-auricular pressure. No blood can yet leave the ventricle, because the intra-ventricular pressure is still lower than the intra-aortic. The tension in the ventricle is rising, but no shortening of the muscle occurs yet. This "*isometric* contraction phase," as it is called, lasts 0·05 second. It is constant under different circulatory conditions and is not affected by the heart-rate.

2. When the intraventricular pressure rises higher it exceeds the intra-aortic, and the semilunar valves open. Rapid ejection of blood occurs, and the volume curve shows that the ventricle is rapidly diminishing in size. As the ventricular muscle shortens, the base of the heart descends and pulls down the auriculo-ventricular ring. The cavity of the auricle is therefore enlarged, causing an abrupt fall of pressure within it. The ventricle and aorta now form one continuous chamber. The aortic pressure therefore passively follows the intraventricular, but at a slightly lower level. In this phase of "maximum ejection" the pressure in the ventricle and aorta rises to its summit.

3. The systolic discharge now lessens and little further change in the volume of the ventricle occurs. More blood is now escaping into the capillaries than is being ejected from the heart, and so the pressure in the ventricle and aorta begins to sink slowly ("reduced ejection phase"). A little blood is possibly left in the ventricles at the end of each systole.

The ejection phase is very variable in length, and is chiefly responsible for the variations in the duration of systole. It lasts 0·2 to 0·25 seconds. The total duration of systole is best estimated in man by accurately timing the interval between the onset of the first and second sound. If the pulse-rate is over 100 per minute, systole lasts less than 0·25 second; between 80 to 100, about 0·25 second; 65 to 80, about 0·28 to 0·3 second; under 65, longer than 0·3 second.

4. Ventricular *diastole* now sets in, and the intraventricular pressure drops very sharply. A backward flow towards the heart occurs in the aorta, and is halted by the closure of the semilunar valves. The pressure within the ventricle continues to fall steeply as the muscle relaxes, but throughout this period ("isometric relaxation phase") the ventricle is a closed chamber.

5. The auricular pressure has been rising throughout the greater part of ventricular systole and now exceeds the intraventricular. The A.V. valves open because of the difference of pressure between the two chambers, and rapid inflow of blood into the ventricle occurs. It is very important to note that during early diastole a large percentage of the total ventricular filling —*i.e.* about 60 per cent.—thus occurs; a good deal of blood can thus enter the ventricles in the absence of any effective auricular contraction as in *auricular fibrillation* (p. 276). As the auricular and ventricular pressures now equalize, little further inflow into the ventricle occurs. If the diastolic pause is a long one, very little increase in ventricular volume takes place ("phase of *diastasis*").

6. Auricular systole now sets in, and the contents of the auricle are driven into the ventricle. On an average the auricular systole only contributes 35 per cent. of the total ventricular output. The exact proportion is dependent on—

(1) Time in diastole at which auricular systole occurs.
(2) Vigour of auricular systole.
(3) Completeness with which the ventricle is already filled.

If the auricle contracts early in diastole it may contribute a considerable amount of blood, up to 60 per cent. of the ventricular output. If it contracts at the end of a long diastole, the ventricle may already be so full that the auricle can contribute relatively little. Auricular systole lasts about 0·11 second.

Auricle.—The pressure changes in the auricle may be briefly summarized (Figs. 75, 80):

1. The *first* positive wave is due to auricular systole. All the fibres of the auricle do *not* contract simultaneously—"fractionate contraction" occurs; the fibres nearest to the S.A. node contract first, and so the intra-auricular pressure begins to rise. At the height of the wave most of the auricular fibres are in action. Late in auricular systole relaxation has begun in most of the fibres; only a few are still contracting, and so the pressure falls.

2. The *second* positive wave is due to bulging of the A.V. valves, which occurs at the onset of ventricular systole (p. 246).

3. A sudden fall of pressure then occurs. This is due to—

(*a*) The negative intrathoracic pressure, which pulls on the relaxed auricle and enlarges its cavity.

(*b*) The ventricular muscle shortens, pulls down the A.V. ring (p. 247), and also helps to enlarge the cavity of the auricle, so that the pressure within it falls.

4. The pressure rises (*third* positive wave) as blood accumulates in the auricle while it is still shut off from the ventricles by the closed A.V. valves. This wave continues beyond the end of ventricular systole to the end of the isometric relaxation phase. When the ventricular muscle relaxes, the A.V. ring moves up again. The cavity of the auricle is thus made smaller, and this helps further to raise the pressure within it. The A.V. valves now open, the auricle empties itself into the ventricle, and the pressure falls rapidly.

The behaviour of the auricle during the cardiac cycle has been compared with that of a concertina. During ventricular systole its cavity is enlarged by the negative pressure in the thorax and the downward movement of the A.V. ring; with the onset of diastole it is compressed by the ascent of the A.V. ring.

Jugular Pressure Tracing.—A good idea of the pressure changes in the right auricle in man can be obtained by recording the pressure changes in the jugular vein. The right vein is employed, because it is in a direct line with the superior vena cava and right auricle. A small metal cup is placed over the vein and connected with a sensitive Marey's tambour. By means of Mackenzie's polygraph, simultaneous jugular and radial tracings can be obtained (Fig. 76).

The jugular tracing shows three positive waves, called *a*, *c*, *v* respectively.

a Wave.—The *a* wave is due to auricular systole. As the pressure in the auricle rises it becomes more difficult for the jugular vein to empty itself, so that the pressure within it is increased. As already mentioned, there is a sleeve of auricular muscle which surrounds the opening of the great veins, and closes the orifice of the superior vena cava during auricular systole by a sphincter-like action. *No* regurgitation of blood into the great veins occurs during auricular systole. The pressure within them rises because of stasis of the blood stream, producing the *a* wave.

c Wave. The *c* wave is probably due to the rise of pressure in the auricle

which occurs at the onset of ventricular systole from bulging of the A.V. valves. Mackenzie thought it was due to the primary wave in the underlying carotid artery (p. 251). The *c* wave can still be obtained, however, if the vein is separated from the artery in animals. Whichever view is correct, there is no doubt that the *c* wave is due to the onset of ventricular systole. The *a*–*c* interval, *i.e.* the interval between the beginning of the *a* and *c* waves respectively, is a guide to the conduction-time of the bundle of His. Strictly speaking, it is the interval between the onset of auricular and ventricular systole. If the *a*–*c* interval definitely exceeds 0·2 second, delayed conductivity of the bundle of His is probably present (Fig. 73).

v Wave.—Like the third positive wave in the auricle, the *v* wave is due

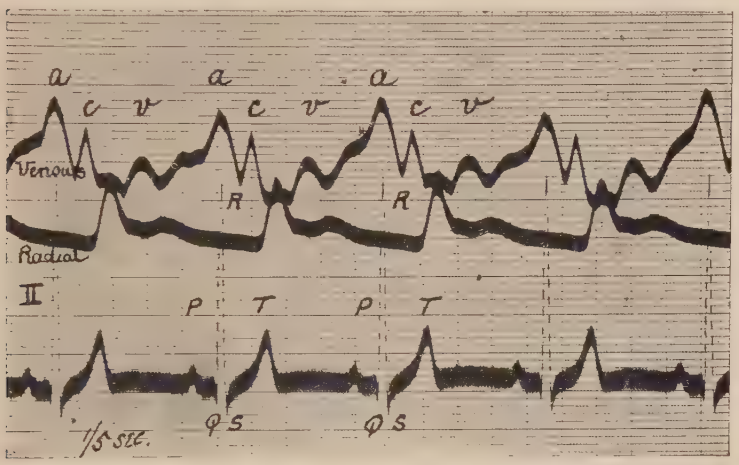

Fig. 76.—Simultaneous Electro-Cardiogram, Venous and Radial Curves from a Young Man. Delay in transmission through the air of the rubber tubing displaces the venous and radial records to the right by approximately 0·03 of a second.—Lewis.

Vertical lines show time in fifths of a second.

to (i) the filling of the auricle while the A.V. valves are shut, and (ii) the upward movement of the A.V. ring which occurs at the end of ventricular systole. The summit of the *v* wave marks approximately the end of ventricular systole.

The negative waves are labelled *x*, *x'*, and *y*, and are caused in the same way as the depressions in the auricular pressure tracing.

The events in the jugular vein naturally occur slightly later than the corresponding events in the auricle. The onset of the *c* wave precedes the primary wave in the radial artery by 0·1 second; the top of the *v* wave precedes the dicrotic notch by a similar interval (see Fig. 76).

The pressure changes in the jugular vein are of importance as giving certain information about the human heart that could otherwise only be obtained by elaborate electro-cardiographic methods. The *a* wave is an indication of auricular systole. It is absent in auricular fibrillation and flutter, when the normal co-ordinated auricular contraction is lost. An

auricular premature contraction is associated with an early *a* wave (Fig. 82); a ventricular extra-systole may coincide in time with the normal auricular contraction and is not therefore preceded by an *a* wave (Fig. 83). The *a–c* interval, as stated, is an index of conductivity in the bundle of His. It is prolonged in bundle lesions (Fig. 73); it is less than normal when the impulse arises in the A.V. node (Fig. 81).

Aortic Pressure Tracing.—1. Two slight *preliminary* vibrations may be noted—(i) due to auricular systole; (ii) due to the isometric rise of tension in the ventricle bulging the semilunar valves outward (Fig. 75).

2. The semilunar valves open 0·05 second after the onset of ventricular systole. Blood now passes from the ventricle into the aorta, and the aortic pressure rises smoothly to a maximum. During the latter part of systole the pressure in the aorta falls slightly. The ventricle is now in its reduced ejection phase and is expelling relatively little blood. The inflow into the aorta from the heart is less than the escape from the aorta and arteries into the capillary bed. It is possible that through the depressor nerve the peripheral resistance is reflexly diminished towards the end of systole, aiding the outflow of blood from the arterial system (cf. p. 283).

3. When ventricular diastole sets in, the pressure in the ventricle drops sharply. This causes a backward flow in the aorta together with a similar drop in aortic pressure termed the *incisura*. The fall of aortic pressure is halted by the closure of the semilunar valves, which causes a slight rebound of the column of blood and is responsible for small after-vibrations. The aorta, which has been stretched during diastole, now recoils. Some of the blood contained within it is driven back towards the heart and helps to close the valves, and some is driven on towards the periphery and helps to set up a second positive wave in the arterial system at the beginning of diastole.

The aortic pressure slowly falls throughout the rest of diastole as the leak into the capillaries continues.

Arterial Pulse.—By the *pulse* is meant the *expansion* and *elongation* of the arterial walls which are passively produced by variations of intra-arterial pressure during systole and diastole. The blood which is suddenly thrown into the aorta during systole is accommodated partly by moving the entire arterial column on at greater velocity, and by distending the arterial wall. This increase of pressure and this arterial distension are transmitted from one segment of an artery to the next, in the form of a wave which is quite independent of the velocity of the blood-flow. The rate of the blood-flow depends on the cross-section of the vascular bed: it is 0·8 to 1·0 metre per second in the aorta and in its larger branches, considerably less in the arterioles, and only about 0·5 to 1·0 *millimetre* per second in the capillaries; it increases steadily in the veins the nearer one gets to the heart, owing to the decrease in their total cross-section. The velocity of the pulse wave is considerably more rapid than that of the blood, as shown by means of the *hot wire sphygmograph* (Bramwell and Hill [1]). This apparatus consists of a fine spiral of platinum wire heated by a battery. Pulses of air from suitable receivers placed over pulsating points on the surface of the body cool the wire and produce alterations in its electrical resistance which is recorded on a string galvanometer; instrumental lag is thus reduced to a minimum. By recording sphygmograms simultaneously from the radial and carotid arteries

[1] Bramwell, Hill, and McSwiney, *Heart*, 1923, vol. x. p. 233.

the velocity of the pulse wave may be accurately determined. The average figures obtained in metres per second at different ages are: age 5, 5·2; age 20, 6·2; age 40, 7·2; age 70, 8·3; with a range of 1 metre above or below these figures. By *elasticity* of an artery is meant the percentage increase in the volume of the artery with each mm. Hg increase in blood pressure. It is related to the velocity of the pulse wave thus: Elasticity $= \frac{12{\cdot}7}{(\text{velocity of pulse wave})^2}$. From these figures the elasticity at different ages can be calculated, *i.e.* age 5, 0·47; age 20, 0·33; age 40, 0·24; age 70, 0·18; *i.e.* there is a *notable decrease*

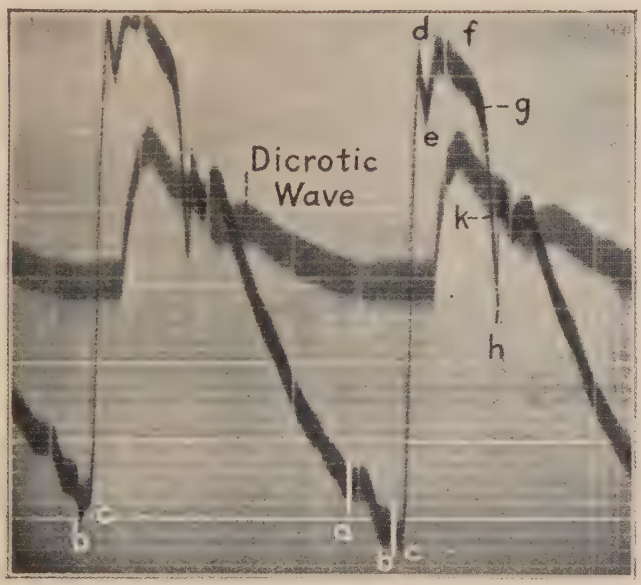

FIG. 77.—Simultaneous Optical Records of Carotid and Radial Pulses.

a, *bc* (on carotid record) = Preliminary vibrations due to auricular systole and isometric ventricular contraction; *cde* = Primary oscillation due to onset of ejection phase; *g* = End of systole; *gh* = Incisura at onset of diastole. Radial pulse is delayed 0·1 second after carotid. (Wiggers, *Circulation in Health and Disease.*)

in elasticity as age advances. This means that with the same cardiac output the blood pressure is raised during systole more in older people than in younger.

The contour of the pulse wave may be recorded by Dudgeon's sphygmograph, Lewis's suspended sphygmograph, and many other methods. Wiggers and Baker have devised a new form of instrument connected with optically recording capsules that probably gives accurate pulse tracings.

CENTRAL ARTERIAL PULSE (*e.g.* in subclavian or carotid arteries) (Fig. 77).—The same preliminary vibrations noted in the aorta may again be detected. A sharp primary oscillation occurs (0·013 to 0·02 second in duration) which coincides with the onset of the ejection phase. It is due to the rapid outflow of blood setting up vibrations in the arterial column. After

this vibration the arterial pressure curve follows the intraventricular, *i.e.* the pressure rises to a summit and then declines. With the onset of diastole there is a marked incisura followed by after-vibrations due to closure of the valves (Fig. 75, Car.).

The arteries form an imperfect conducting system. The pressure variations noted are modified in their transmission along the vessels owing to friction and interference by *reflected* waves which may be set up at each arterial bifurcation

Radial Pulse.—When the radial artery is reached, the preliminary oscillations have completely disappeared. The upstroke is delayed 0·1 second after that in the carotid and is more gradual and smoother. No notch on the upstroke can now be detected. The tops of the waves are rounded and their amplitude is smaller. The sharpness of the incisura is reduced and is replaced by a rounded *dicrotic* dip or notch. The end of systole is approximately indicated by this notch. It is noted that the *primary* wave (or percussion wave) in the radial rises first, and then falls towards the end of systole, as does the corresponding wave in the large arteries. The initial rise (expansion of the artery) is due to the fact that blood is being pumped out more rapidly by the heart than it is escaping into the capillaries; the later fall is due to the reduced ejection phase of the ventricle delivering less blood than is passing out through the arterioles (which may be reflexly relaxed) (p. 283). When the dicrotic notch is thus present on the downstroke, the pulse is called *catacrotic* in character. It is generally agreed that the *dicrotic wave* which follows the notch represents a modification of the vibrations set up by the closure of the aortic valves and the rebound of the blood from these curtains (Figs. 75, 76, and 77).

Little significance can be attached to the form of the pulse in records not obtained by optical means.

A large primary wave may be due to (i) large output; (ii) slow rate; (iii) low peripheral resistance. A small primary wave is due to (i) small output; (ii) high peripheral resistance from increased arterial tone or impaired elasticity of the vessels (Wiggers).

Occasionally a break or notch occurs on the ascent which is termed the *anacrotic* notch. Its significance is not yet clearly understood. It is observed in cases in which the aorta is compressed, aortic stenosis, arteriosclerosis, etc.

It can be shown in a circulatory scheme that the descending limb of the pulse curve falls more steeply if the diastolic pressure is low, the arterial wall thick, or if aortic regurgitation is present. Similarly, after injection of nitrites or stimulation of the depressor nerve to produce relaxation of the arterioles, and in aortic disease in man (p. 267), a rapid downstroke is observed.

REFERENCES

Wiggers.—*Circulation in Health and Disease*, 2nd Edn., Philad., 1923.
Mackenzie.—*Study of the Pulse*, London, 1902; *Diseases of the Heart*, London, 1925.

Heart Sounds.—The heart sounds may be magnified and recorded by placing a microphone in circuit with a string galvanometer.

1. First Heart Sound.—This begins 0·022 second after the commencement of the R wave of the electro-cardiogram (*q.v.*) (see Fig. 78). It precedes the primary wave in the carotid artery by 0·12 second. The first heart sound consists of a few small introductory vibrations which are said to occur at the end of auricular systole. Then five or six main vibrations occur with the onset of ventricular systole. A few short final vibrations occur during the ejection period. The duration of the sound is 0·05 to 0·15 second.

It is agreed that the sound is due to two factors :

i. Friction of the interlacing bands of the contracting ventricular muscle.

ii. Closure of the auriculo-ventricular valves. The intensity of the first sound varies directly with the tension developed in the heart during the isometric period and does not depend on the output of the heart. It was noted above that the main vibrations occurred early in systole.

2. Second Heart Sound.—This occurs precisely at the onset of diastole,

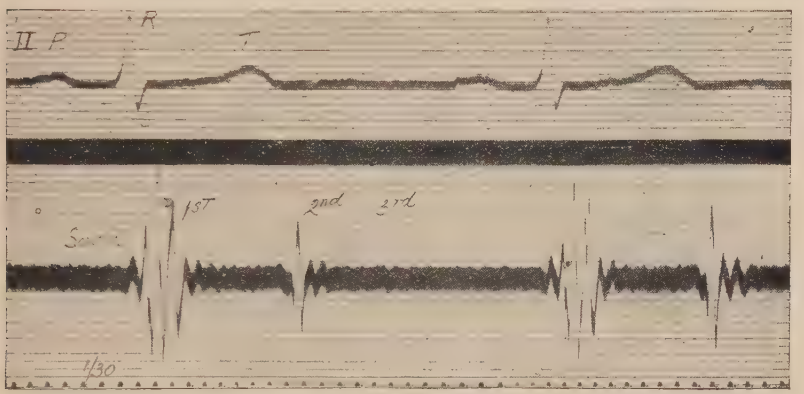

Fig. 78. Simultaneous Electro-Cardiogram and Heart Sound Curve from a Normal Man.

The figure shows the time relations of the electro-cardiogram to the beginnings of the 1st and 2nd heart sounds. Points on a vertical line are simultaneous.—Lewis.

and is due to the closure of the semilunar valves at the base of the heart. Its intensity varies with the blood pressure in the great vessels at the *onset* of diastole (Wiggers).

A third heart sound, which is not audible during ordinary auscultation, may be detected in magnified records. It is said to be due to *after-vibrations in the aortic valves* following their closure (Einthoven).

Reduplication of the First Sound may occur in apparently healthy individuals. In pathological conditions the reduplication is due to an added group of vibrations which precede the first sound. It may be due to an audible auricular systole when the auricle is hypertrophied or the P–R interval is unduly prolonged. Asynchrony of the ventricles can only occur in branch bundle lesions. It must be a rare cause of reduplication, and experimentally it does not lead to this condition.

Reduplication of the Second Sound is frequently attributed to asynchronous closure of the semilunar valves ; the evidence, however, goes to show that the added element is really an accentuated third sound.

The Rate of the Heart

Nerve supply of the heart (cf. pp. 120, 123).

1. The Vagus.—The connector fibres arise in the dorsal nucleus of the vagus and run in the vagus trunk to end in nerve cells in the sino-auricular and auriculo-ventricular nodes. The right vagus chiefly supplies the S.A. node, and the left vagus ends mainly in the A.V. node. From the nerve cells present in the two nodes, a second relay of fibres arises to supply the auricles, the bundle of His, and the base of the ventricles. The apex of the ventricles is said not to receive any vagal fibres.

The vagus exerts a continuous restraining action on the rate of the heart. This is proved by the acceleration which follows section of these nerves in most animals, or paralysis of the nerve endings by atropine in man. The degree of vagal activity, or " vagal tone " as it is called, is probably the chief factor controlling the rate of the human heart at rest.

Stimulation of the peripheral end of the cut vagus proves that the nerve can depress every part of the cardiac mechanism.

i. *S.A. Node.*—The rate at which impulses are elaborated here is diminished, and so the whole heart is slowed (right vagus).

The vagus is thought to delay the recovery process in the node, and so a longer period elapses before it again reaches a sufficient degree of excitability to generate a fresh impulse.

ii. *Auricle.*—There is considerable diminution in the force of contraction of both auricles. The duration of systole is greatly shortened, and so the refractory period is similarly diminished.

iii. *Bundle of His.*—Conductivity is impaired to a varying extent. First the P–R interval of the electro-cardiogram is prolonged ; then occasional impulses from the auricle fail to be transmitted through the bundle, and 2 : 1 or other regular relationship between the auricular and ventricular rates is established. Conductivity may be entirely abolished, and auricles and ventricles thus become completely dissociated. As already noted, the ventricle is so " accustomed " to being driven from the auricle that, should its functional connections with that chamber be suddenly destroyed, it remains quiescent for a brief period and does not beat at all. In this way the vagus may produce temporary ventricular silence. The ventricle as a rule soon resumes beating at its own slower independent rate. It should be noted that such " idio-ventricular rates " are outside nervous control altogether. Block of one or other branch of the bundle of His may be produced, with characteristic alterations of the electro-cardiographic record (p. 236).

iv. *Ventricle.*—There may be slight diminution in the force of the ventricles, but this effect is not striking.

Summary.—The vagus thus—(i) slows the whole heart ; (ii) produces varying degrees of heart block or arrests the ventricle altogether ; (iii) diminishes the force of contraction of the chambers of the heart ; (iv) the refractory period and the duration of systole are shortened.

Effect on the Blood Pressure.—As the heart is slowed and its force lessened, the output of the heart is greatly reduced, and the blood pressure falls rapidly (Fig. 79). Within a few seconds of commencing vagal stimulation the blood pressure may sink almost to zero, and remains low. On ceasing to

stimulate the nerve, the blood pressure mounts rapidly and may exceed the initial pressure and then return to normal.

Several reasons may be adduced to account for the excessive after-rise of blood pressure:

i. During vagal stimulation the circulation is so inadequate that an element of asphyxia supervenes, which stimulates the vasomotor centre and constricts the arterioles.

ii. The auricles and great veins become engorged with blood which the feebly acting heart cannot dispose of. As soon as the ventricles resume functioning normally, the great diastolic filling stretches the fibres, and so the force and output of the heart are increased.

"*Vagus Escape.*"—Vagal stimulation may be continued and in spite of

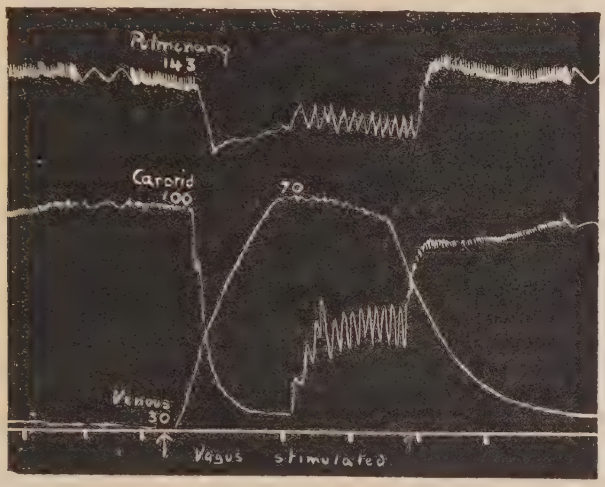

FIG. 79.—Vagus Escape.

Record of pulmonary and venous pressure (in mm. H_2O) and carotid pressure (in mm. Hg). 1 mm. of tracing=3 mm. pressure. Peripheral end of vagus stimulated (first arrow), causing arrest of heart. Pulmonary and carotid pressures both fall, venous pressure rises abruptly. When the venous pressure has risen to 70 mm. H_2O ventricular escape occurs, which brings about a partial recovery of the arterial pressure and a slight decrease of the venous. On cessation of stimulation (second arrow) there is typical recovery. (McDowall, *Journ. Physiol.*)

this the pulse may quicken, and the blood pressure rises. Two factors are possibly at work:

i. The onset of vagus escape is often associated with high pressure in the great veins leading to the right auricle. This stimulates sensory fibres which pass up the (intact) vagus to the cardiac centre reflexly to accelerate the heart (Bainbridge reflex, p. 258). This reflex *competes* with the effects of the arterial stimulation of the other (cut) vagus and may overcome it, causing the heart to increase in rate (McDowall)[1] (see Fig. 79).

ii. In some cases complete heart block is produced, and the ventricle assumes its independent rate, which is in no way affected by the vagus nerve.

In the human subject—

[1] McDowall, *Journ. Physiol.*, 1926, vol. lxi. p. 131.

(*a*) Compression of the vagus by firm pressure in the middle or lower third of the neck may inhibit the heart. The carotid artery may, however, have to be obliterated first, with serious after-effects.

(*b*) Pressure on the eyes through the closed lids, if firmly maintained for a few seconds to a degree to cause much discomfort, may reflexly inhibit the heart.

The *nature* of the vagus effect cannot yet be adequately explained.

(i) Gaskell suggested that the vagus produces the reverse effect to that of ordinary motor nerves—it hastens the building up of the precursor of the muscular contraction, *i.e.* it produces a state of *anabolism*.

Tissues which are undergoing katabolic or breakdown processes are "negative" compared with resting parts. By analogy, an anabolic area should become "*positive*" relative to unaffected regions. This was demonstrated by Gaskell. If the auricle of the tortoise is severed from the sinus, it comes to a standstill. The apex of the auricle is damaged and the galvanometer reveals that it is "negative" compared with the unaffected base of the auricle. The vagus is stimulated. It cannot influence the injured area but the normal base becomes more "*positive*," so that a greater difference of electric potential is now found between it and the injured spot.

(ii) "*Humoral*" theory of vagus action.—In the isolated frog's heart it has been shown that as a result of vagus stimulation a chemical substance is liberated which appears in the lumen of the ventricle and which will inhibit another heart to which it is applied; it will also produce vagus effects in other organs—*e.g.* it causes contraction of the stomach (Loewi). (Similarly sympathetic stimulation is said to give rise to a substance which can augment and accelerate another heart.)

Drugs.—Atropine paralyses the vagal nerve-endings in the heart muscle. Nicotine painted on the heart first stimulates and then paralyses the synapses in the nodes of the heart, but stimulation of the post-ganglionic fibres is still effective.

The Sympathetic.—The sympathetic connector cells lie in the lateral horn of grey matter of Th3, 4. The fibres pass to the stellate ganglion in animals, and to all three ganglia (superior, middle, and inferior) of the cervical sympathetic in man, where they relay. The excitor fibres pass in the cardiac branches to the heart.

Stimulation of the sympathetic increases the rate and force of contraction, *i.e.* it accelerates and augments the heart beat.

Regulation of the Heart-Rate.—There is believed to be a cardiac centre in the floor of the fourth ventricle in the region of the vagus nucleus. It consists of two portions:

i. *Cardio-inhibitory* centre, which presumably is part of, or closely related to, the dorsal nucleus of the vagus.

ii. *Cardio-accelerator* centre, in the same region, which must have connections with the thoracic cord in order to control the sympathetic supply of the heart.

The rate of the heart is affected by—

1. Impulses from the higher centres.
2. Respiration.
3. Reflexly (*a*) from the heart: (i) arterial side; (ii) venous side.
   (*b*) from other parts.
4. By the quality and quantity of the blood reaching the brain.
5. By body temperature.
6. By the intracranial pressure.

1. Higher Centres.—Emotion may readily affect the pulse-rate: in states of excitement, the heart usually quickens; sudden shocks may slow or even arrest the heart. The common form of *fainting* attack provoked by emotion or long standing is partly due to a vagal effect. Nervous women, convalescents, and the subjects of aortic regurgitation are particularly liable to be affected. The attack is ushered in by unsteadiness, giddiness, and dimness of vision. The heart's action gradually becomes slower, and the pulse-rate may fall to 50 or 40. At the height of the attack, pallor and sweating may be prominent symptoms. The systolic blood pressure may sink to 50 or 60 mm. Hg, owing largely to independent depression of the vasomotor centre.

2. Respiration.—In most adults, during quiet breathing, the heart-rate does not alter. During voluntary deep breathing, all normal people show quickening of the heart with inspiration, and slowing with expiration. This respiratory variation occurs in many healthy children with quiet breathing, and is referred to as *sinus arrhythmia*. It has no pathological import whatever.

The respiratory variations are due to alterations in vagus tone which take place with each phase of the breathing, probably as a result of afferent impulses from the lungs; it has also been suggested that as inspiration increases the venous return it raises the pressure in the right auricle and thus reflexly accelerates the heart. Sinus arrhythmia is abolished by paralysing the vagi with atropine.

Irregular Variations.—Periodic variations in the rate of the heart may occur independently of respiration and without apparent reason. They may be noticed in convalescence from acute fevers and after the administration of digitalis (Lewis).

3. Reflexly from the Heart.—*A.* Arising in the wall of the left ventricle and the root and arch of the aorta is a nerve called the *depressor* nerve, which may run separately (rabbit) or in the vagus trunk to the medulla. It reflexly slows the heart by increasing vagus tone, and relaxes the arterioles by inhibiting the vasomotor centre.

These effects may be studied by stimulating the central end of the cut vagus nerve or of the depressor nerve itself.

(1) The rate of the heart diminishes; the blood pressure sinks fairly rapidly and usually remains depressed for as long as the nerve is stimulated and often for some time after.

(2) The cardiac slowing is due to reflex stimulation of the vagi, and is abolished when the vagi are divided or paralysed by means of atropine.

(3) The fall of blood pressure is not solely due to slowing of the heart, for it still occurs, though to a less marked degree, when the vagi are cut. It is then due to reflex inhibition of the vasomotor centre. The vascular relaxation affects chiefly the splanchnic and cutaneous blood vessels. Thus if the volume of the kidney or of a loop of intestine be recorded by means of a plethysmograph, the organ is found to swell owing to dilatation of its arterioles.

Mode of Action of the Depressor Nerve.—The depressor nerve is the main afferent supply of the heart. Other afferent fibres pass into the posterior nerve roots of Th1–3 (p. 137). The depressor nerve protects the heart against the evil effects of any sudden excessive rise of blood pressure. Should this occur under *resting* conditions, the depressor nerve is stimulated because of

the stretching of the heart and aorta. The blood pressure is reflexly lowered and the heart is slowed. It may be noted that in muscular exercise the heart-rate increases in spite of the raised blood pressure as the auricular reflex is then predominant owing to the high venous pressure.

A current of action is said to pass up the depressor nerve with every beat of the heart. The stretching of the aorta which occurs at the height of systole may stimulate the depressor nerve and cause reflex relaxation of the arterioles. This may account in part for the fall of intra-aortic pressure during the latter part of systole. As the peripheral resistance is opened up, blood escapes more readily from the arterial system into the capillary bed (p. 252).

In *aortic regurgitation*, the left ventricle is hypertrophied, the output of the heart is large, and the systolic blood pressure is abnormally high (*e.g.* 180 mm. Hg.). This probably causes an exaggerated depressor reflex at the height of systole, great arteriolar relaxation, and the pressure in the arteries falls rapidly towards the end of systole. This is claimed to be partly responsible for the *collapse* of the pulse (cf. p. 267) and the low diastolic pressure which are characteristic of the condition (Stewart).

Abnormal and excessive stimulation of the depressor nerve results in pain which is referred to the distribution of the cervical nerves. The phenomena of *angina pectoris* have been thought to be due in some cases to an exaggerated visceral reflex, of which the depressor nerve forms the chief afferent path. Disease of the aortic arch (Allbutt), or overstretching of the heart by a sudden increase in the blood pressure, stimulates the depressor nerve, and the normal protective reflex may be carried to an extreme and harmful degree. Severe or agonizing pain is experienced. Reflex interference with the heart's action occurs, as shown by alteration in the electro-cardiographic curves during an anginal attack (*e.g.* branch bundle block). The heart may be so disturbed that death may ensue. To abolish the reflex phenomena of angina, section of the depressor nerve in man has been advised and carried out.[1]

B. Nerve fibres arise from the *venous* side of the heart—*i.e.* the right auricle and the root of the great veins—and pass in the vagus trunk to the medulla. These nerve endings are stimulated when the venous pressure rises. As a result, the vagus is reflexly depressed and the sympathetic accelerator fibres are reflexly stimulated so that the rate of the heart increases (Bainbridge). In muscular exercise the venous return is greatly increased, and so the pressure in the right auricle would be expected to rise. In man, even after brief exercise the venous pressure is found raised, but falls rapidly to normal. By means of this "auricular reflex" the heart is accelerated during exercise, and is thus enabled to get rid of all the blood reaching it.[2]

In *heart failure* engorgement of the right auricle often occurs, and rise of the venous pressure (p. 288). The auricular reflex may thus be set up, and accounts in part for the rapid pulse found in this condition.

C. Stimulation of *sensory* nerves may produce varying effects. Stimulation of the central end of the fifth nerve and of the splanchnic nerve causes slowing of the heart. A blow on the abdomen and irritation of the mucous

[1] As discussed on pp. 137 and 244, coronary thrombosis is the underlying pathological lesion in many cases of angina.

[2] For other factors accelerating the heart in exercise, see p. 353.

membrane of the nose produce similar results. Most painful stimuli quicken the heart.

4. (*a*) Lack of oxygen—*anoxæmia*—accelerates the heart, and is another factor in the production of the rapid pulse of heart failure. An increased pulse-rate is thus found in anæmic states, carbon monoxide poisoning, after hæmorrhage, and at high altitudes. Anoxæmia first causes an apparent increase in the force of the heart beat, but the vigour later dies down, though the heart accelerates till just before the end.

(*b*) Excess of CO_2 when of moderate extent also quickens the heart. In larger amounts it poisons the bundle of His, produces heart block and a slow ventricular rate.

5. A rise of *body temperature* acts directly on the sino-auricular node and quickens the rate of impulse formation. The cardio-accelerator centre is also stimulated.

6. A rise of *intra-cranial pressure* from any cause—*e.g.* in *raised blood pressure*, late in cerebral tumour—directly stimulates the vagus centre and slows the heart.

It may be noted that *adrenaline* injected into an intact animal in large doses raises the blood pressure, and the heart is reflexly slowed through the vagi. After section of the vagi, adrenaline quickens the heart from direct action on the sympathetic endings. Large doses of adrenaline (1·5 c.cm.) in man quicken the heart secondarily to increasing the metabolic rate (p. 129).

Summary.—The rate of the heart depends on *vagus tone*, *respiration*, and the *metabolic activities* of the body. A sudden rise of blood pressure may slow the heart. Emotion produces varying effects.

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The Output of the Heart

The output of the heart (*circulation rate*) is perhaps the most important constant in the body, but its determination in the human subject is difficult, and in spite of much research no simple reliable method is yet available.

Methods.—1. Douglas and Haldane's Method.—It was first pointed out by Fick that the output of the heart could be determined if the following facts were known:

I. CO_2 content of the mixed venous blood, *e.g.* 56 c.cm. per cent.
II. CO_2 content of the arterial blood, *e.g.* 52 c.cm. per cent.
III. CO_2 output per minute, *e.g.* 300 c.cm.

It follows that every 100 c.cm. of venous blood reaches the lungs carrying 56 c.cm. CO_2, and leaves with 52 c.cm. CO_2, *i.e.* gives off 4 c.cm. CO_2. Therefore 300 c.cm. CO_2 are given off by $\frac{100}{4} \times 300 = 7{\cdot}5$ litres, which is the circulation rate through the lungs per minute and consequently the output of right and left ventricles.

In animals, arterial blood can be easily obtained, and puncture of the right heart gives us a sample of the mixed venous blood, and thus the gas contents

can be directly determined. In man these methods are not readily available. It is no use collecting blood from a *cutaneous* vein and determining its CO_2 content. There is every reason to believe that the composition of the venous blood differs in the various regions of the body with the degree of local tissue activity. We need to know the composition of the *mixed* venous blood, which is only found in the right heart and the pulmonary artery. Indirect methods must therefore be employed.

I. Alveolar air analysis gives the tension of CO_2 in the alveoli, which we believe to be the same as that found in arterial blood. By reading the tension obtained (*e.g.* 40 mm. Hg) off the CO_2 dissociation curve for blood (p. 348) the CO_2 content of arterial blood is determined.

II. The CO_2 output per minute is easily found by collecting the expired air in a Douglas bag (p. 314), and measuring its volume and determining its composition.

III. If we could determine the CO_2 tension of the mixed venous blood, we could determine its CO_2 content from the dissociation curve. Douglas and Haldane have devised the following method for estimating the CO_2 tension of mixed venous blood and consequently the output of the heart:

If we guessed the venous CO_2 tension, we could add enough CO_2 to the air in the alveoli to raise the CO_2 tension there to the same level. The venous blood passing through the lungs would be thus exposed to a CO_2 tension identical with its own, and therefore would neither take up nor give off any CO_2. If the breath were held for five seconds, the alveolar air at the end of that period would have the same CO_2 content as at the beginning; and this alveolar CO_2 tension then represents the venous CO_2 tension.

Four gas bags are taken and each is filled with 30 litres of air. Enough CO_2 is added to raise the CO_2 content of the bags above that present in normal alveolar air (which is 5·6 per cent.), *e.g.* to 6, 6·5, 7·0, 7·5 per cent. respectively. A deep expiration is made to the outside air to empty the lungs of all but the residual air. Two or three deep breaths are made in and out of the first bag, ending up with a maximum inspiration which is held for two seconds. In this way the air in the lungs and the bag are thoroughly and uniformly mixed, and the alveolar CO_2 content is raised. One and a half litres of air are expired sharply down an alveolar air sampling tube, and the last air breathed out is collected for analysis. This is the *first* alveolar sample. The breath is held for five or six seconds. A maximum expiration is made and a *second* alveolar air sample is collected. After a few minutes' pause the same procedure is gone through with the other bags. The results are thus tabulated (from Douglas and Priestley):

	CO_2 per cent. in Air in Bag.	CO_2 per cent. in First Alveolar Sample.	CO_2 per cent. in Second Alveolar Sample.
1	6·39	6·31	6·37
2	6·66	6·43	6·45
3	7·00	6·72	6·68
4	7·60	6·92	6·78

In the first two determinations the alveolar CO_2 rose during the time the breath was held. Five seconds holding the breath is too short a period for equilibrium to be reached between the venous blood and the air in the alveoli, and all one can say is that the CO_2 tension in the alveoli was *lower* than in the venous blood, so that CO_2 diffused from the blood into the lungs. In the third and fourth experiment the alveolar CO_2 fell; *i.e.* the initial alveolar CO_2 pressure was higher than that of the venous blood, and so CO_2 diffused into the blood. The venous CO_2 tension lies between 6·45 and 6·68 per cent. recorded in the second and third observations. The mean, 6·55 per cent., was equivalent (Barom.=754 mm.) to a tension of 46·3 mm.

In reading off the CO_2 content, the dissociation curve for *oxygenated* blood is employed (p. 348). Under the conditions of the experiment the venous blood at the end of 5 seconds is oxygenated (as it was exposed to the high oxygen content of the alveoli), but has given off no CO_2. The CO_2 dissociation curve for the individual need only be determined if great accuracy is aimed at; for ordinary purposes the curve given on p. 348 may be employed.

By similar methods the *oxygen* tension of the mixed venous blood could be determined. Under conditions of rest, the mixed venous blood contains on an average about 15 c.cm. O_2 per cent., the arterial blood 18·5 c.cm. O_2 per cent., *i.e.* the amount taken up by each 100 c.cm. blood is about 3·5 c.cm.

2. Hill's Method.—The elaborate method just detailed is obviously not available when strenuous work, such as running, is carried out, but the Fick method in a modified form can give information about the cardiac output even in violent exercise. If the O_2 content of the arterial blood and of the mixed venous blood and the oxygen consumption per minute are known, the output of the heart can obviously be calculated. The arterial oxygen content can be deduced from a knowledge of the hæmoglobin content of blood obtained from a finger prick: suppose the blood contains 15 grm. Hb. per 100 c.cm. (equivalent to 107 per cent. Hb. on the Haldane hæmoglobinometer), then as 1 grm. Hb. can unite with 1·34 c.cm. O_2 when fully saturated, the O_2 capacity of the blood is $15 \times 1{\cdot}34 = 20$ c.cm.; the arterial blood can be assumed to be about 95 per cent. saturated, so that the O_2 content of the blood is 19 c.cm. The O_2 consumption is readily determined by the Douglas bag technique. A. V. Hill has shown that the O_2 consumption in exercise may reach 4 litres and even 5·9 litres per minute. The exact O_2 content of the *mixed venous blood* is guessed at, and not directly determined. During bicycle work, when the O_2 consumption is 2 to 3 litres per minute, the O_2 content of the blood may be reduced by 65 per cent., and the venous blood contain only 7 or 8 c.cm. per cent. In more strenuous work it is justifiable to presume that the blood is even more extensively reduced, *i.e.* the venous O_2 content is perhaps 4 c.cm. per cent; the blood leaving the muscles is almost completely reduced, but that from the skin, brain, and viscera still contains fair amounts of oxygen. Each 100 c.cm. of blood in passing through the lungs thus takes up 15 c.cm. O_2 (O_2 content rising from 4 to 19 c.cm.). If 4 litres of O_2 are consumed, the circulation rate is $\frac{100}{15} \times 4000 = \underline{27 \text{ litres}}$ approximately.

If the O_2 consumption is 5·9 litres, the circulation rate may exceed 40 litres.

If the pulse-rate is 180 per minute, the stroke volume is between 170 to 220 c.cm.

3. Ethyl Iodide Method.—Numerous attempts have been made to determine the output of the heart by methods which depend on the inhalation of foreign gases—*e.g.* Krogh's nitrous oxide method or Henderson's ethyl iodide method. The former method has been generally abandoned; as the latter is still on trial it will be briefly outlined. Ethyl iodide is a liquid which volatilizes readily. It can be estimated when present in quite small concentrations in air. 0·3 c.cm. of ethyl iodide are volatilized in a large spirometer for each 100 litres of air present. The subject breathes from the spirometer through valves; specimens of inspired, expired, and alveolar air are collected, and the pulmonary ventilation per minute is determined. According to Henderson the "partition coefficient" between alveolar air and blood is 2, *i.e.* the concentration of ethyl iodide in the blood under these conditions is *twice* that in the alveolar air. The ethyl iodide concentration in the arterial blood is thus obtained by multiplying the alveolar air figures obtained by two. It is further claimed that the ethyl iodide inhaled is completely destroyed in the tissues so that none returns in the venous blood. The method of calculation is seen from the following example:

Pulmonary ventilation = 8 litres per minute.
Ethyl iodide in inspired air = 1 mg. per 100 c.cm.
Ethyl iodide in expired air = 0·5 mg. per 100 c.cm.

$$\therefore \text{ Ethyl iodide absorbed in 1 minute } = \frac{1-0{\cdot}5}{100} \times 8000 = 40 \text{ mg.}$$

Ethyl iodide in alveolar air = 0·25 mg. per 100 c.cm.
∴ ,, ,, in arterial blood = 0·25 × "partition coefficient"
= 0·25 × 2 = 0·5 mg. per 100 c.cm.
,, ,, in venous blood = 0 (assumed by Henderson).

0·5 mg. ethyl iodide are absorbed by 100 c.cm. blood flowing through lungs;

$$\therefore \text{ 40 mg. ethyl iodide are absorbed by } \frac{100}{0{\cdot}5} \times 40 = \underline{8 \text{ litres}}$$

= *output per minute.*

This method has the advantage of not needing the co-operation of a trained subject. Unfortunately two of the statements made by Henderson, and on the validity of which the method depends, have not been confirmed: Wright and Kremer[1] found that varying amounts of ethyl iodide may return in the venous blood, up to 70 per cent.; and further that the partition coefficient between alveolar air and blood varied in different experiments between 2 and 7.

4. Heart-Lung Preparation (Starling).—This preparation is useful for studying the output of the heart under conditions where most of the factors can be modified at will. The thorax of an animal is opened and artificial respiration is carried out. The aortic arch is tied beyond the origin of the innominate artery. By means of a cannula the blood is led from the innominate artery to an artificial peripheral resistance which consists of a thin rubber tube enclosed in a glass tube, in which the pressure can be raised to any desired extent. The blood is warmed and returned to the right auricle, and sent by the right ventricle through the lungs and thus back to

[1] Wright and Kremer, *Journ. Physiol.*, 1927, vol. xiv, p. 107.

the left heart. Variations of pulse-rate are prevented by section of the vagi. The output of the heart can be measured directly by collecting the blood for a given time after it has passed through the peripheral resistance.

The output of both ventricles under *normal* conditions is exactly the same. The blood pumped out by the left ventricle depends on the amount it receives from the right side of the heart *via* the pulmonary circulation. The output of the right heart depends on the *venous return*. How the return of blood from the tissues to the heart is regulated is not fully understood, but the principal factors are the following:

1. The contractions of the *skeletal muscles* squeeze the veins contained within them and drive the blood on towards the heart. The veins possess valves which prevent regurgitation of the blood in the intervals between the muscular contractions.[1]

2. With each inspiration there is an increased *negative pressure* in the thorax which aspirates blood towards the heart. The diaphragm descends, raises the intra-abdominal pressure, and so squeezes blood out of the splanchnic veins.

3. A slight positive pressure is present in the capillaries (6 to 10 mm. Hg) and veins which can propel blood on towards the heart. Relaxation of the arterioles raises the capillary pressure locally, and so aids the venous return.

4. *Gravity* assists the venous return from parts above heart level, but greatly hinders the return from the dependent regions.

5. Changes in *blood volume*: the venous return is diminished by a decrease in blood volume as after hæmorrhage.

6. *Capillary tone*: normally most of the capillaries in any organ are closed or quite narrow. If all the capillaries over a considerable area become patent and widely dilated they can accommodate a large proportion of the blood volume and little is left to return to the veins. The venous return is greatly reduced for this reason in histamine poisoning (p. 290) and in surgical shock.

One of the results of an increase in the venous return can be studied in the denervated heart-lung preparation, in which alterations in rate do not take place. It is found in the heart-lung preparation that by increasing the venous return the output per beat is increased proportionately. The greater *initial length* of the cardiac fibres at the beginning of systole results in more forcible contraction, so that greater amounts of blood are discharged at each beat ("law of the heart"—Starling). If the fibres are overstretched then a more feeble contraction results, the output is diminished, and the heart does not empty itself effectively. The pressure in the heart rises very little during the diastolic filling, because the heart fibres elongate and adapt themselves to accommodate the blood which is entering. In valvular incompetence, *e.g.* mitral or aortic regurgitation, there is excessive accumulation of blood behind the leak, *e.g.* in the left auricle and left ventricle respectively. The fibres are more stretched and contract more powerfully. The continuous overwork results in overgrowth and *hypertrophy* of the corresponding chamber of the heart.

In the *innervated* heart the increased venous return is partly dealt with by *acceleration* (p. 258).

At *rest*, the minute output is from 5 to 8 litres; the output per beat

[1] There is some evidence that the veins are actively contractile.

(*stroke volume*) is from 70 to 120 c.cm., according to the subject studied. According to Henderson, the stroke volume in a vigorous adult is related to the body *weight*, and varies from 1·3 to 1·8 c.cm. per kg. (*stroke index*). In women it may be as low as 1·1 or 1·2 c.cm. The pulse-rate is more closely related to the *surface* area of the body. Sitting at complete rest for two hours lowers the circulation rate considerably, *e.g.* from 7·9 to 5·3 litres, and the stroke volume diminishes, *e.g.* from 116 to 87 c.cm. The O_2 consumption per minute, of course, is lower too, *e.g.* 274 against 301 c.cm. (Barcroft).

Relation of Output to Metabolism.—The metabolic activities of the body are limited by the oxygen supplies. Each litre of O_2 employed in the combustion of food-stuffs makes available 4·8 calories [1] (on an average). We would expect the minute output of the heart (*circulation rate*), and consequently the oxygen supplied to the tissues, to be regulated by the *metabolic rate*, and this is found to be the case. Bodily activity means more vigorously contracting muscles, more powerful respiratory movements, relaxed arterioles, and raised capillary pressure. The heart deals with the increased venous return in mild exercise either (i) by accelerating the pulse-rate, or (ii) by increasing the stroke volume, or both methods may be employed.

In addition, the increased demands of the tissues for oxygen are met by abstracting more O_2 from the blood reaching the tissues, *i.e.* the coefficient of utilization ("arterial-venous oxygen difference") is raised; and the venous blood leaves more extensively reduced (cf. p. 334).

In *strenuous exertion*, such as severe running, the minute output may reach 30 to 40 litres; the pulse-rate rises to 150 to 180 per minute, and the stroke volume may be as large as 170 to 220 c.cm. (A. V. Hill). The mixed venous blood is extensively reduced (O_2 content=3·5 c.cm.), and the arterial-venous oxygen difference (18·5 minus 3·5) is 15 c.cm. per cent.

If the blood volume is taken to be 5 litres, it is obvious that, at rest, an amount equal to the blood volume is discharged each minute from each ventricle. In strenuous exertion, over *six* times the blood volume (about 8 gallons) may pass through each ventricle per minute. This last figure probably represents the maximum possible effort of the heart. As indicated on pp. 154 and 156, owing to the changes in metabolism in *exophthalmic goitre* and *myxœdema* corresponding changes in the circulation rate are encountered. It is somewhat difficult to see how alterations in the metabolism (apart from exercise) produce the modifications in the venous return which must of necessity precede an alteration in cardiac output. It may be supposed, however, that if the metabolism is increased the arterioles in the more active tissues are relaxed with corresponding rise of capillary and venous pressure which propels blood more rapidly to the heart.

Effect of Gravity.—In passing from the lying to the standing position, the stroke volume diminishes constantly and to a considerable extent. In one subject the output was halved on standing up. Apparently we are not able to overcome the effects of gravity completely, and in the erect position the venous return is impaired. The recumbent position is consequently of great value in flushing all the tissues with abundant supplies of oxygen, though, paradoxically, the work of the heart is greater. We can understand

[1] The large calorie is always referred to unless otherwise stated. It equals 1000 small calories, and is the amount of heat required to raise 1 litre of water 1° C.

why fainting may occur during standing for long periods, especially in hot rooms.

Effect of Cold.—If a subject is exposed for 15 minutes to a temperature of – 1° C. in a cold passage, the metabolism is stimulated, the O_2 consumption rises (*e.g.* from 348 to 412 c.cm. per minute), and as would be expected the circulation rate rises (*e.g.* from 6·7 to 7·6 litres per minute). The pulse-rate usually slows, and so the stroke volume may increase (*e.g.* from 91 to 124 c.cm.).

Effect of Warmth.—The subject was exposed for one hour to a temperature of 40° C. External heat causes relaxation of the blood vessels of the skin, both arterioles and capillaries. A much greater blood-flow to the skin results, which enables adequate amounts of heat to be given off from the body by evaporation and radiation. The metabolic rate does not rise, but the circulation rate is increased (by 20 to 50 per cent.) by accelerating the pulse to 90 or 100. The skin is accommodating increased amounts of blood, and so the output of the heart must be raised to enable adequate amounts of blood to reach the internal organs and the muscles. The blood leaving in the skin veins has a very high oxygen content. It is not metabolic activity but *temperature* regulation which brings about this high blood-flow to the skin. The " arterial-venous oxygen difference " is less than normal, *i.e.* the mixed venous blood has a higher O_2 content than normal.

Relation of Output to Blood Pressure.—An increase in cardiac output raises, and a diminution in output lowers, the blood pressure.

If the peripheral resistance is suddenly raised, the heart falters for a few beats and fails to empty itself adequately. More blood is left behind after each beat. This, in conjunction with the venous return, results in elongation of the heart fibres, more forcible contraction, and emptying of the heart in spite of the increased resistance.

Relation of Heart Rate to Output.—If the venous return is constant, increasing the rate of the heart cannot raise the output per minute (circulation rate). The heart cannot eject more blood than it receives, and at its normal rate it empties itself effectively and keeps the venous side of the circulation depleted. If the venous return increases, the heart quickens (through the auricular reflex) so as to empty itself completely. In muscular exercise mechanical factors (squeezing of veins, respiratory movements) drive more blood back to the heart ; in any condition of heightened *metabolism* more blood reaches the heart because of the arteriolar relaxation, and the heart quickens because of the auricular reflex.

Atropine increases the pulse-rate but does not alter the circulation rate per minute, because the output per beat is diminished.

Paroxysmal Tachycardia.—In this condition the heart may suddenly accelerate to 150 to 200 per minute. In one case studied, the output per minute fell from the normal level in that subject, 5·6 litres, to 2·5 litres, and the output per beat from 77·5 c.cm. to about 15 c.cm. (Barcroft). This illustrates how a very rapid pulse-rate cripples the circulation. Diastole is too brief to allow proper filling of the heart. Each beat only discharges a small amount of blood. The rest period is very short, and so the heart becomes fatigued and signs of heart failure become manifest.

Heart Block.—If the heart is slowed down, *i.e.* to 30 per minute in complete heart block, an adequate circulation is maintained by greater

diastolic filling of the ventricles and a greater output per beat. If the heart slows further, the circulation rate becomes inadequate for the needs of the body. Fainting and loss of consciousness may occur (p. 239).

Mitral Incompetence.—In experimental mitral lesions, it has been shown that little if any regurgitation into the auricle occurs during the isometric contraction phase of the ventricular systole. This is apparently due to the shortness of this phase (0·05 second), and also to the fact that the intraventricular pressure is relatively low, ranging up from a few mm. Hg to only 60 mm. Hg (see Fig. 80).

The principal backflow occurs during the *ejection* phase, when the ventricular pressure is very high, and continues for 0·08 second into diastole. The intraventricular pressure then falls below the intra-auricular, and the A.V. valves open. The auricular volume and pressure increase markedly through-

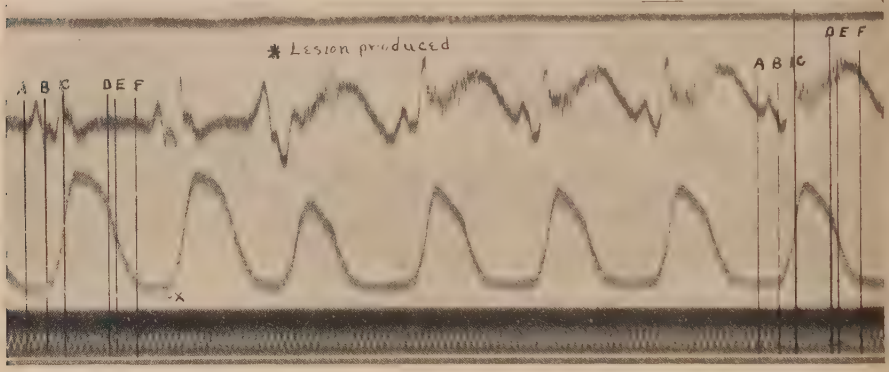

Fig. 80.—Simultaneous Records of Auricular (upper) and Ventricular (lower) Pressure Changes in Experimental Mitral Incompetence.

AB=Auricular systole; BC=Second positive wave in auricle and isometric ventricular contraction; CD=Ejection phase of ventricle; E=Closure of aortic valves; EF=Isometric ventricular relaxation. At × mitral incompetence produced. Note that AB, BC, in auricular record are little altered. During ventricular ejection, CD, auricular pressure is markedly raised by regurgitating blood, as also indicated by vibrations on curve. Regurgitation continues through early part of diastole. Time in 0·02 second. (Wiggers and Feil, *Heart.*)

out the period of regurgitation. Because of the regurgitation, the systolic discharge of the left ventricle is first reduced. The initial result of an experimental mitral regurgitation is that the systolic and diastolic blood pressure fall and the pulse pressure decreases. Compensation, however, is soon effected.

When the A.V. valves open, the left auricle, which is engorged with blood (which has come from the right heart and through the mitral leak), discharges an *increased* amount into the left ventricle. This results in greater initial length of the ventricular fibres and more forcible contraction. Some of the blood regurgitates into the left auricle, but enough is pumped into the systemic arteries to maintain an adequate circulation.

The augmented volume of blood in the left auricle is accommodated by expansion of the left auricle and of the pulmonary veins. The pressure in the pulmonary bed probably only rises during the ventricular "ejection phase" when regurgitation is occurring (Wiggers).

Mitral Stenosis.—There is a progressive diminution in the output per beat to 35 to 45 c.cm. This is partly due to the obstruction at the mitral valve and partly perhaps to failure of the heart muscle. Auricular systole becomes progressively more important in introducing blood into the ventricle, as little blood can flow passively out of the auricle. The rate of the heart is increased, but only partial compensation is thus achieved. The circulation rate may be only 4·2 to 5·3 litres per minute. Later the circulation can only maintain the resting metabolic requirements and no more. If auricular fibrillation sets in, the circulation rate may fall to 3·5 litres per minute.

Aortic Regurgitation.—In aortic regurgitation the systolic blood pressure is high. This is due to the increased output of the left heart, which discharges not only the blood received from the veins but also the amount which has leaked back into the left ventricle during diastole. The diastolic blood pressure is low and the pulse pressure is increased.

Cases of arterio-venous aneurysm—*i.e.* where there is an abnormal communication between an artery and a vein—present many of the arterial phenomena of aortic regurgitation. In both conditions blood leaks out of the arteries by other than the natural pores provided by the capillaries. Certain differences are to be expected, because in aortic regurgitation the leak is confined to diastole and in the other condition the leak occurs throughout the cardiac cycle.

The following arterial phenomena are common to both conditions and are abolished by closing the anastomosis in arterio-venous aneurysm. They are therefore due to the abnormal leak which is present:

1. Low diastolic pressure (cf. 3).

2. "*Water hammer*" character of the pulse, *i.e.* a sudden impact is felt by the palpating hand. This sensation is due to the rapid upstroke in the initial phase of the primary wave, which may also be of greater amplitude than normal. The phenomenon is much exaggerated by holding up the arm vertically.

	Time from Beginning of Upstroke to Half-way Point	
Horizontal position of arm	Normal, 0·039 sec.	Aort. Reg., 0·027 sec.
Vertical position of arm	Normal, 0·045 sec.	Aort. Reg., 0·017 sec.

(Lewis and Drury.)

The speedy ascent is due to the abnormally low diastolic pressure. The ventricle meets with very little resistance; the blood passes out of it very rapidly, and so the aortic pressure rises with abnormal speed. *Visible pulsation* in the arteries of the neck is due to the same reason, *i.e.* sudden distension of the underfilled vessels.

3. *Collapse of the Pulse.*—After the sudden impact just described, the pulse rapidly falls away. According to Stewart, the fall occurs during *systole* (when *no* regurgitation is occurring), *i.e.* it precedes the dicrotic notch. He attributes it to a reflex vaso-dilatation of the peripheral arterioles (cf. p. 258). According to Wiggers, there is a steep fall which *follows* the dicrotic notch, and therefore occurs during diastole. It may be caused by the reflux of blood into the ventricle which is then occurring.

4. In the horizontal position, the systolic pressure in the *leg* is higher than in the arm. This is not believed to represent a true rise of internal pressure. There is increased tone of the arterial *wall*, which may diminish

the lumen of the vessels and is a compensatory phenomenon to help to keep blood out of the dependent parts. This arterial hypertonus has to be overcome before obliteration of the vessel can begin, and thus high readings for the systolic pressure are obtained. If the limb is warmed the hypertonus disappears, and the systolic pressures in leg and arm become the same (Hill).

A case showing all the arterial signs enumerated is described by Lewis as one of "free" aortic regurgitation. The degree of leak must be equal to that present in arterio-venous aneurysm when the same arterial phenomena are present. The leak, it is found, may equal or exceed 50 per cent. of the total cardiac output.

Capillary pulsation is present in aortic regurgitation, and is seen as clear rhythmic expansion of the capillary loops with each beat of the heart (Sumbal).

The pulsation affects the minute skin venules too. Capillary pulsation is a *physiological* phenomenon and occurs in the skin and mucous membranes whenever the arterioles are sufficiently dilated, provided that the pulse pressure is normal and capillary and venule tone is not increased. It is to be commonly observed in young people at room temperatures of 17° to 20° C., after soaking the hand in water at 45° C., and in the facial flush produced by amyl nitrite. Capillary pulsation should therefore be associated with dilated arterioles, which permit the pulse to reach the minute skin vessels, rather than with any particular morbid condition (Lewis).

It should be noted that the regurgitant stream raises the intraventricular tension in diastole and impedes the filling of the ventricle through the mitral orifice. The filling of the coronary arteries is impeded (p. 243). The nutrition of the heart muscle suffers, and dilatation results.

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New Rhythm Centres.—In the normal heart several centres of rhythm formation are potentially active, but the centre which generates an impulse most rapidly sets the pace of the heart. This is normally the S.A. node.

1. If the S.A. node is destroyed or cooled, while the A.V. node is warmed, or if the right vagus is stimulated to depress the S.A. node and at the same time the left sympathetic is stimulated to heighten the excitability of the A.V. node, it is found that the A.V. node becomes the dominating centre. The impulse passes to the auricle and ventricle, and the two chambers contract simultaneously. The P–R interval is greatly diminished; the P wave is inverted or buried in the substance of the R. Any reduction of the P–R interval below normal limits is regarded as indicating the origin of the impulse in the A.V. node. In view of the great structural resemblance between the S.A. and A.V. nodes, it is not surprising to find a high degree of rhythmicity in the A.V. node (see Fig. 81).

2. If the ventricle is suddenly cut off from the auricle, it may remain

quiescent for a time. It then resumes beating, at first slowly and then more rapidly. If the ventricle is gradually dissociated from the auricle, the new rhythm attains its full rate very soon. The ventricular impulses now arise in the bundle of His just below the injury (cf. p. 239). This idio-ventricular rhythm is *not* controlled by the vagus.

3. *Occasional* spontaneous beats may arise anywhere in the substance of the auricle. True rhythmic function—the ability to initiate and *maintain* the heart beat over prolonged periods—is only present in the nodes and the junctional tissues.

Ectopic Beats (Extra-Systoles).—1. If the auricle is stimulated during

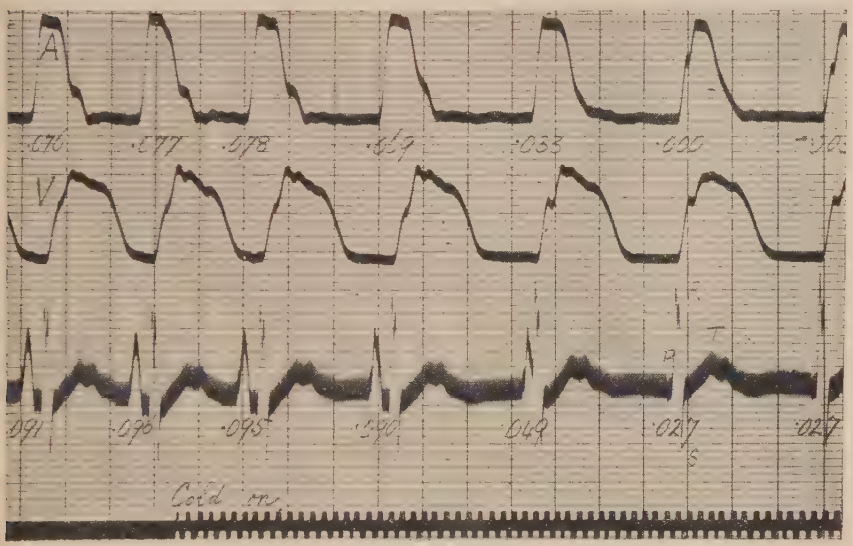

FIG. 81.—Myocardiographic Curves (A = Auricle; V = Ventricle) and Electro-Cardiogram from Lead II. showing the Effect of applying Cold to the Sulcus Terminalis in a Dog.

When cold is applied (see signal) the S.A. rhythm slows; at the fifth cycle there is escape of the A.V. node, though the auricle, being already in systole, does not respond, *i.e.* the auricle responds to the impulse from the S.A. node, but the ventricle responds prematurely to the A.V. nodal impulse (the P-R interval is reduced to 0·049 second). Subsequent cycles show fully established A.V. rhythm. The auricle is represented in the electro-cardiogram by a minute dip (inverted P wave) preceding the upstroke of R. The P-R interval is now reduced to 0·027 second, and the interval between auricular and ventricular contraction is reduced almost to nothing: the two chambers are contracting simultaneously. The auriculo-ventricular and P-R intervals are given in decimals of a second.—LEWIS.

diastole after its refractory period has passed, it responds by a *premature* contraction. The impulse reaches the ventricle, which contracts too. The rate of recovery of the bundle is slower than that of the other parts of the heart, and so if an impulse reaches it prematurely, conduction along it is delayed. The P–R interval, therefore, is prolonged. The P wave shows a degree of abnormality which is greater the farther the stimulus is applied away from the S.A. node, because, as stated, the height and direction of the P wave are an indication of the way in which the excitation process has spread over the auricle. The P wave may thus be inverted, isoelectric, or

abnormal in the details of its configuration. The ventricular complex QRST is normal. The next auricular impulse arising in the S.A. node appears after a pause equal to the normal diastolic period or a little in excess of it (see Fig. 82).

2. If the ventricle is stimulated after the refractory period has passed, *i.e.* after the end of systole, it responds by contracting. As the ventricle obeys the "all-or-none" law it responds to the maximum of its ability if the stimulus is adequate. The actual force of the contraction depends on the extent to which the ventricle has recovered from its previous contraction, and the degree of filling which has taken place. If the ventricle is stimulated early in diastole, the contraction it gives is feeble and may be insufficient to

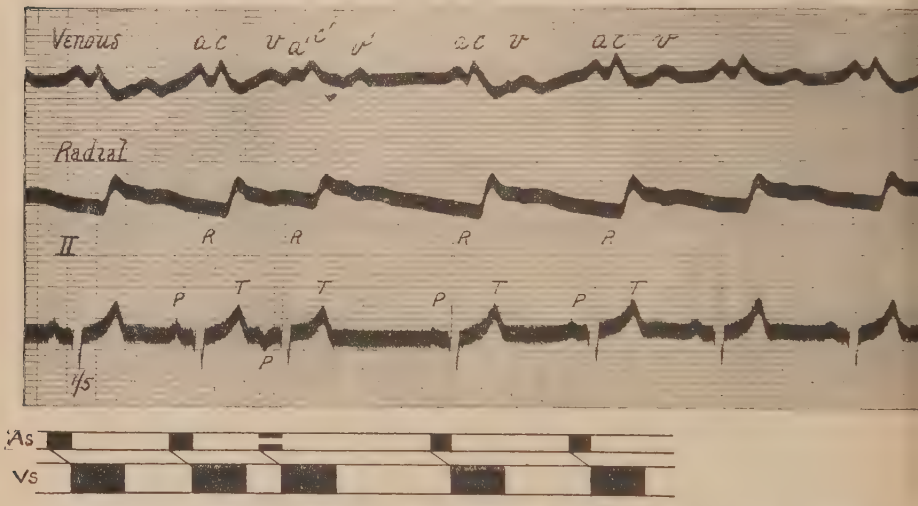

FIG 82.—Simultaneous Venous, Radial, and Electro-Cardiographic Curves exhibiting Auricular Extra Systoles in a Patient, and a Diagram representing the Disturbed Mechanism.—LEWIS.

The third beat is the premature one; the P wave is inverted and follows very closely on the preceding T wave; the succeeding ventricular complex is normal. There is a premature pulsation at the wrist. The premature auricular wave *a'* precedes in a normal fashion *c'*, *v'*. A pause longer than the normal diastolic period follows the premature beat in this case.—LEWIS.

open the semilunar valves. The premature beat then only gives rise to the first heart sound and is not accompanied by arterial pulsation at the wrist. If the premature contraction occurs later in diastole, the ventricle may discharge its contents. As the ventricle has not had time to become completely filled, the output during this premature beat is less than normal, and the pulsation felt at the wrist is small.

Following the extra-systole is a long pause, so that the "extra-systolic" cycle and the "returning" cycle are equal to two normal cycles. The reason for this "compensatory pause" is simple. The auricular impulse following the extra-systole finds the ventricle in a refractory condition, and no response is obtained. The ventricle must therefore wait for the succeeding impulse before contracting (see Fig. 83).

The way in which the excitation process spreads in the artificially stimulated ventricle is interesting. The impulse spreads radially over the surface of the muscle in all directions. It also penetrates the thickness of the ventricular wall to reach the endocardium and invade the specialized Purkinje tissue. This tissue then transmits the impulse rapidly over its own side of the heart. The contralateral ventricle receives the impulse later by continuity of the muscle substance of the two sides of the heart. The electro-cardiographic deflections consequently show a similarity between extra-systoles and branch bundle lesions. A right ventricular extra-systole resembles a

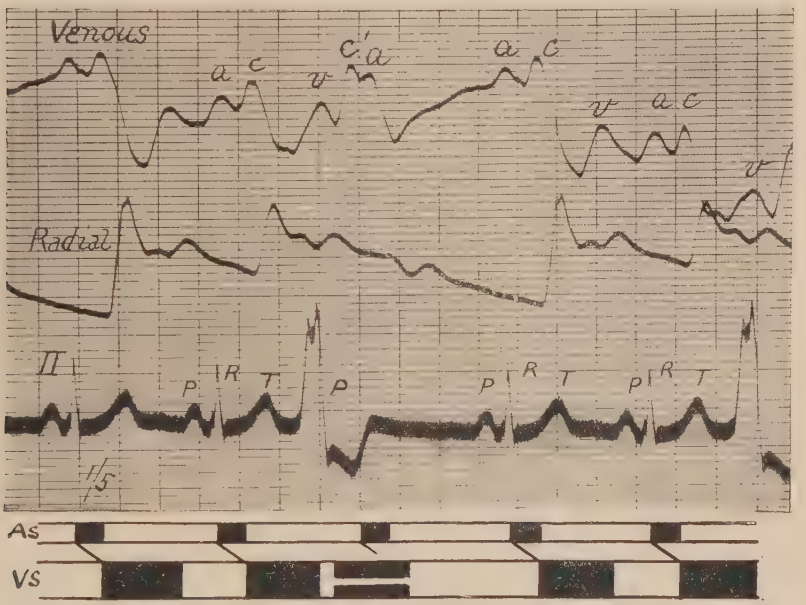

Fig. 83.—Simultaneous Venous, Radial, and Electro-Cardiographic Curves from a Patient, showing an Extra Systole arising in the Right Ventricle.—Lewis.

A diagram placed below illustrates the mechanism of the heart over the period of the disturbance. The premature ventricular complex is abnormal in character: the P wave is buried in, instead of preceding, the ventricular complex. Similarly *c'* wave is premature and precedes the *a* wave. The pause following the premature beat is longer than normal; the auricular rhythm is undisturbed.

dextro-cardiogram (due to a left branch bundle lesion), because in both cases the right ventricle is excited first, and fairly completely, before the left ventricle is involved (Fig. 83). Similarly, a left ventricular extra-systole resembles the lævo-cardiogram (due to right branch bundle lesions). In this way the site of origin of a premature ventricular contraction can be ascertained by study of the electro-cardiographic record (cf. Fig. 72).

Response of Auricle to Rapid Stimulation.—As the rate of the auricle increases, the duration of systole and of the refractory period both diminish (see Table, p. 272).

When the auricle is stimulated at about 250 to 300 per minute a phenomenon called the *partially refractory state* develops. This is a hypothetical

Auricular Rate.	Length of Cycle.	Absolute Refractory Period.
100 per minute.	0·6 second.	0·2 second.
150 ,,	0·4 ,,	0·17 ,,
290 ,,	0·21 ,,	0·11 ,,

condition in which it is thought that some muscle fibres at any given moment are responsive, while adjacent fibres are refractory. An artificial stimulus applied to the muscle results in some groups of fibres reacting and others failing to respond. If a large part of the auricle responds, a big beat is obtained; when a small area reacts, a small beat results. The fibres which respond at one beat are not sufficiently recovered and fail to react to the succeeding stimulus, so alternate large and small contractions result. With more rapid rates of stimulation, *e.g.* about 450 per minute, the refractory period is *increased*, and is longer than the interval between succeeding stimuli. A state of 2 : 1 response of the auricle results, *i.e.* each second stimulus finds the auricle in a refractory state, and so a contraction results from alternate stimuli only (see Table *infra*). Stimulation of the vagus shortens the duration of systole, and so diminishes the refractory period. The 2 : 1 response is abolished, and the auricle responds to each stimulus even at rates as high as 450 per minute.

	First Phase : Rates up to 290 per Minute.	Second Phase : Rates 290–380 per Minute.	Third Phase : Rates 380 to 450 or over per Minute.
Force . .	Beats uniform.	Beats irregular in force, or alternate large and small beats.	
Refractory period.	Gradually reduced, and constant from cycle to cycle.	Steady or rising. Irregular in length from cycle to cycle.	Longer than interval between stimuli. Transient or constant 2 : 1 response of whole auricle.

(After Lewis.)

The refractory period of the ventricle is longer than that of the auricle, and 2 : 1 response develops when stimulation occurs at 350 per minute. The A.V. node has a still longer refractory period, and cannot transmit more than 270 impulses per minute.

Efficient *conduction* in the auricle depends on the excitation process meeting responsive tissue which can transmit the impulse farther. When the auricle is stimulated at high rates, conduction in the auricle is slowed. It will be recalled that considerable areas of the auricular wall may be in a refractory state when the excitation process reaches them. These form areas of obstruction, and the impulse instead of flowing smoothly must wind

about irregularly to seek out portions of tissue which have recovered. Instead of taking the shortest possible route between two points, it must wander around by devious paths seeking islets which have passed out of the refractory condition. The rate of conduction in the auricle when it is stimulated at high rates may fall to 500 mm. per second (normal = 1000 mm.).

The Ring Experiment (Mines, Garrey).—If a ring of muscle is taken and a point upon it, A, is stimulated, a wave of excitation develops which spreads equally in both directions, till it reaches the opposite side of the ring at B. When muscle is in the grip of the excitation process, it is completely refractory, so when the crests of the excitation waves reach the point B, they

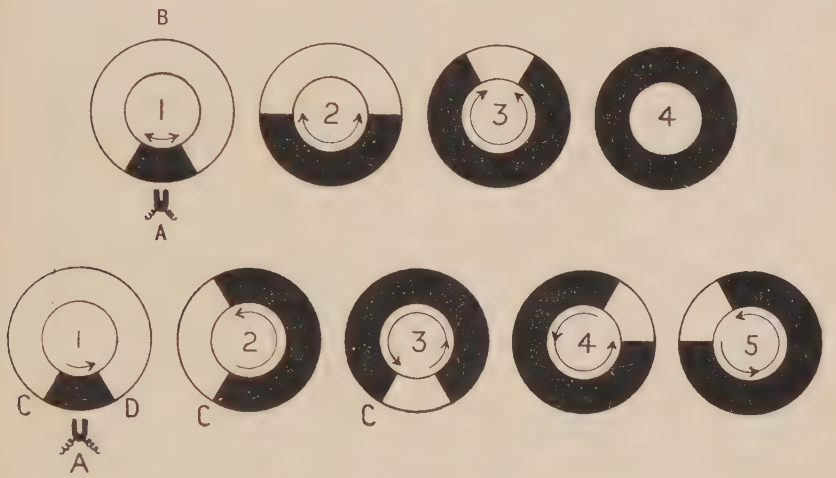

FIG. 84.

UPPER LINE (1–4).

Diagram illustrating Progress of Single Wave passing through a Ring of Muscle as a result of stimulating it at point marked by electrodes. Black portion of ring represents refractory state.

LOWER LINE (1–5).

Diagram to illustrate the Establishment of a Circus Movement in a Ring of Muscle. The ring is stimulated at A and the wave spreads to C and D. At C it is blocked, but from D it continues round the ring. When it arrives at C, the refractory state has passed off and so it continues to travel round the circle.—LEWIS.

are faced by unresponsive tissue, and can proceed no farther. The wave of excitation is thus arrested, and the active state gradually passes off from the whole ring of muscle.

If the rate of stimulation is increased, we have already learnt (p. 271) that at a certain critical rate, just before 2 : 1 responses are obtained, a condition called the " partially refractory " state develops. Certain parts of the muscle have fully regained their responsiveness, others are still refractory when each stimulus falls on the muscle. In the case of a ring of muscle, the point A may respond and the impulse spreads out from it. At C, however, it finds itself faced by an area which has not recovered sufficiently and so the impulse in this locality is extinguished. The region D happens

to be responsive, and so the impulse spreads in that one direction only. If conditions happen to be suitable, it finds responsive tissue before it, and travels on as a single crested wave right round the ring. When the point C is reached (which was refractory before) it is found to be responsive, and so the wave travels on to the original starting-point A. This point too has recovered from its refractory condition, and so a fresh cycle begins. The wave of excitation can thus go on circulating round the ring for minutes or hours. The terms "*circus movement*" is used to describe the wave which travels continuously round and round in one direction.

To establish a circus movement the following conditions must be fulfilled:

1. An area of refractoriness must be present to prevent the passage of the impulse in one direction.

2. The originally refractory area must have recovered when the excitation process reaches it for the second time.

Conditions which favour the development of the circus movement are: (i) large ring; (ii) slow rate of conduction; (iii) short refractory period. These three factors are largely interdependent. We should fix our attention on the head of the advancing wave and the gap of responsive tissue in front of it. If the length of the ring is 100 mm. and the wave travels at the rate of 500 mm. per second, each circuit is completed in 0·2 second. If the refractory period of the muscle is 0·15 second, then any point on the muscle recovers 0·05 second before the circus reaches it again. In 0·05 second the wave travels 25 mm. (rate=500 mm. per second). In the case of any part of the ring the crest of the wave is 25 mm. away when it passes out of the refractory state. If conduction is slower, or the refractory period is shorter, the gap is lengthened. If conduction is faster or the refractory period is longer, the gap is diminished and may disappear. The excitation process is stopped by refractory tissue, and the circus movement comes to an end.

Tending to abolish Gap.	Tending to increase Gap.
Shorter path.	Larger path.
Quicker conduction.	Slower conduction.
Longer refractory period.	Shorter refractory period.

(Lewis.)

The conception of a "circus movement" has greatly assisted the understanding of two disturbances of cardiac rhythm, namely, *auricular flutter* and *auricular fibrillation*.

Auricular Flutter.—This is a clinical condition in which the auricle beats from 230 to 350 times per minute with considerable regularity and for prolonged periods. This state can sometimes be induced experimentally in the following manner. The auricle is stimulated by induction shocks at from 300 to 600 times a minute. For a few seconds the auricle responds very rapidly. The stimuli are then withdrawn. Instead of resuming its original rate, the auricle may continue to beat rapidly, but not at the rate at which

the induction shocks had been thrown in. It is found that a circus movement has been set up in the auricle (Lewis).

Normally (cf. p. 281) the excitation process in the auricle arises in the S.A. node and travels regularly over the surface of both auricles like a ripple over a pond. It spreads down the tænia to reach the inferior vena cava region, passes across to the left auricle, and invades the appendages from base to tip. The excitation process, having invaded the whole auricle, gradually dies down to await the initiation of a new impulse by the S.A. node.

Fig. 85 (left) illustrates what is happening in auricular flutter. Electrodes placed on various points on the auricle are connected to galvanometers and signal the arrival of the excitation process in the subjacent tissue.

The excitation is first noted in the region of the inferior vena cava opening. It is then traced up the tænia to reach the superior vena cava region. It then runs down the intra-auricular band to reach the left auricle and so down to the I.V.C. region again. A circus movement appears to be going on continuously round the ring of auricular tissue, joining the openings of the

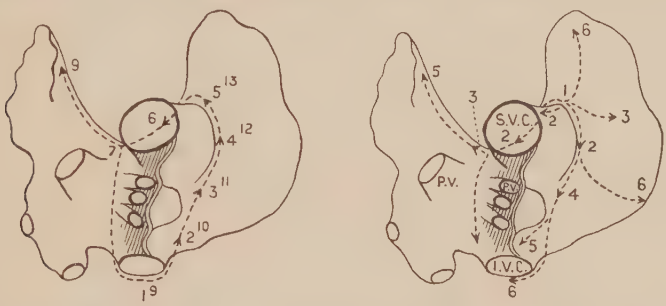

Fig. 85.—Natural Outline of Dog's Auricle, showing paths of the excitation wave (broken lines) when the heart beats naturally (right) and during flutter (left). The numbers indicate the approximate order in which the various parts of the musculature received the excitation wave.—Lewis.

inferior and superior venæ cavæ. Instead of the auricle being stimulated from a single point (the S.A. node), there is a sort of circulating centre of impulse formation. As the wave travels round the ring, the excitation process spreads out to involve the rest of the auricular muscle. The auricle contracts once, each time the wave completes one circuit of the ring.

The path of the circus movement varies. It may be clockwise or anticlockwise in direction. It may encircle one vena cava opening or other natural orifices like the mitral or the tricuspid openings (Lewis).

The production of flutter is difficult experimentally, because it depends on several factors being present at the same time. When the auricle is stimulated very rapidly it passes into the *partially* refractory state (p. 271), in which at any moment some areas are responsive and others are not. When the stimuli are stopped, an impulse which is travelling in the auricle may find itself blocked in one direction, but is able to travel through responsive tissue in another direction. By the time it reaches the originally refractory area, it may find it responsive, and so the wave goes on circulating round and round.

The factors controlling flutter are those which control the circus movement.

1. Duration of effective refractory period: the crest of the excitation process must find responsive tissue in front of it.

2. Circuit time of the wave must, of course, be longer than the refractory period of the muscle.

3. Length of the central circus path. In man the rate of the auricle in flutter is between 240 and 350 per minute. Each circus movement is therefore completed in 0·17 to 0·25 second. When the auricle beats at these high rates, the refractory period is reduced to 0·12 to 0·11 second (normal is 0·2 second). The rate of conduction in the auricle is reduced to 500 mm. per second (normal is 1000 mm. per second). As already explained (p. 273), conduction is slowed because the excitation wave is obstructed by small barriers of unrecovered tissue which lie in its path. The wave must consequently take a slightly sinuous path round these obstacles. The outline of the ring traversed by the circus movement is slightly irregular and the effective conduction rate is half the normal.

	Rate.	
	240 per Minute.	350 per Minute.
Cycle (duration of each circus movement) .	0·25 second.	0·17 second.
Absolute refractory period of muscle. .	0·12 „	0·11 „
Rate of conduction	500 mm. per second.	
Length of path (circumference) . .	(0·25×500) 125 mm.	(0·17×500) 85 mm.
∴ Diameter of ring	40 mm.	27 mm.

The figures for the diameter of the ring are slightly in excess of the diameters of the natural orifices of the auricles. The size of the "gap" is thought to be about 15 to 20 mm. If the rate of conduction is speeded up, or the refractory period is prolonged, the gap is abolished and the circus movement comes to an end.

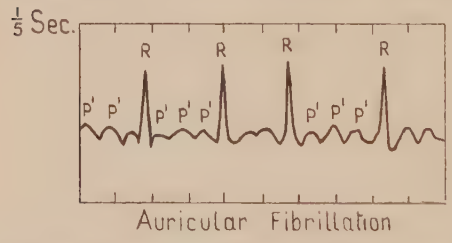

Fig. 86.—Note irregular spacing of Ventricular Complexes (R).

The A.V. bundle cannot transmit impulses at very high rates, and so the *ventricular* rate is half or even one-quarter of the auricular rate.

Auricular Fibrillation.—In auricular fibrillation the auricle is beating about 450 times per minute. To the naked eye, no co-ordinate auricular contraction is visible. A fine irregular tremulousness on the surface of the auricle is all that can be seen. The condition can be produced experimentally by rapid stimulation of the auricle as in the case of flutter, and here, too, the

new rhythm sets in after the stimulation is stopped. The presence of a circus movement can be demonstrated. The details are as follows :

Auricular rate . .	450 per minute.
Duration of each cycle .	0·13 second.
Rate of conduction . .	500 mm. per second (p. 273).
Length of path (circumference) . .	(0·13×500) 65 mm.
Diameter . . .	20 mm.
Absolute refractory period of auricle . . .	0·09 second.

Much of the auricular substance has a longer refractory period than 0·09 second. The size of the gap must be extremely small, the " crest of the wave riding close to, and interlacing with its own wake " (Lewis).

Most of the auricle at any moment is in a state of complete or partial refractoriness. The crest of the wave must take a coarsely sinuous path which may vary somewhat from circuit to circuit in the search for responsive tissue. Impulses do not reach the outlying parts of the auricle with any regularity, as they are obstructed by refractory areas. Consequently the A.V. node is stimulated at irregular intervals. In addition, the A.V. bundle does not transmit all the impulses reaching it. The ventricular rate is much less than that of the auricle (*e.g.* 130 per minute), and the beats are completely irregular and bear no constant relationship to one another. The beats may similarly be large or small, depending on how much blood is present in the ventricle at the beginning of each systole. This rapid irregularity greatly interferes with the output per minute, which falls to less than 4 litres, and each beat of the heart discharges only 30 to 40 c.cm.

Influence of Digitalis and Quinidine.—*Digitalis* in adequate doses further depresses conductivity in the bundle of His. Fewer impulses therefore reach the ventricle, which has more time to fill owing to the more prolonged diastole. The output and the force of the heart are increased, and the muscle has a longer rest period. The condition of the *auricle* is not altered in any way.

Quinidine given in suitable doses is capable of abolishing the circus movement present in flutter and fibrillation in a proportion of cases, and may restore the normal auricular rhythm. Quinidine produces the following effects on the heart :

1. It lowers the rate of impulse formation in the sino-auricular node considerably.
2. It depresses conductivity in the auricle, ventricle, and bundle of His.
3. It produces partial paralysis of the vagus.
4. It lengthens the refractory period of heart muscle. The effects on conductivity and the refractory period are those that particularly concern us in connection with the circus movement. A reduced rate of *conduction* tends to slow the rate at which the circus movement is travelling, and thus allows more time for the tissue in front to recover and become responsive. The circus movement thus becomes more firmly established. A sufficient lengthening of the *refractory* period, on the other hand, reduces the size of the responsive gap or abolishes it. The tissue is still refractory when the circus

movement reaches it, and so the circulating wave is arrested. If the effect on the refractory period predominates, the circus movement comes to an end, and normal rhythm is re-established. If the conducting factor predominates the circus continues, but is slowed down (Lewis).

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Ventricular Fibrillation may be produced as follows:

1. Application of a strong constant or faradic current to the ventricle.
2. Ligation of a coronary artery (cf. p. 244).
3. Administration of toxic substances, including excessive doses of digitalis.
4. When low percentages of *chloroform* vapour are inhaled, the irritability of the ventricle is enhanced to a precarious degree. Injections of minute doses of *adrenaline*, stimulation of a sensory nerve, or some inconspicuous and unnoticed influence, or even a fresh dose of stronger vapour, may precipitate fibrillation (Goodman Levy).

Sequence of Events.—i. Ventricular extra-systoles arise in one or many foci.

ii. Rapid, almost regular, small undulations of the ventricle occur.

iii. Fibrillation sets in, and co-ordinate contractions of the heart fibres cease. The heart dilates and the blood pressure falls to zero. Inspection shows that the ventricle is convulsed by minute quivering; one area is contracted and the adjacent one is relaxed. The electro-cardiogram shows large irregular oscillations.

Clinically, fibrillation of the ventricle has been recorded in the *dying* heart. The earlier stages (i. and ii.) have been recovered from. Ventricular fibrillation is the mechanism of sudden and unexpected death, with loss of pulse, pallor passing to cyanosis, and a few gasping respirations (Lewis).

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VI

THE CIRCULATION

Blood Pressure.—Peripheral resistance—Vasomotor centre—Higher centres—Quality and quantity of blood to brain—Reflexes—Ductless glands—Respiration—Metabolites—Vaso-dilator fibres—Methods of measuring—Normal range—Hypertension—Hypotension.

Venous Pressure.—Measurement—Influence of respiration, heart failure.

Capillaries. — Structure — Independent contractility — Action of Histamine — Nerve supply—Hormone control—Capillary pressure—Vascular responses of skin—"Triple response" and "H"-substance — Effect of heat, cold, and light.

Traumatic Shock.—Factors concerned in secondary shock.

Tissue Fluid and Lymph. — Filtration — Properties of membranes — Osmotic pressure—Tissue activity—Formation and removal of fluid—Maintenance of blood volume — Removal from serous cavities and subcutaneous tissues — Œdema—Abnormal permeability—Urticaria — Venous obstruction — Cardiac œdema—Renal œdema—Lipoid nephrosis—Other causes.

THE BLOOD PRESSURE

By the blood pressure is meant the lateral pressure exerted on the walls of the vessels by the contained blood. It varies as the *product* of the *cardiac output* and the *peripheral resistance*. The factors controlling cardiac output have already been discussed (pp. 263–265, see also p. 240); the peripheral resistance alone will be considered here.

Peripheral Resistance.—The peripheral resistance consists of the tonically contracted arterioles in the splanchnic area and skin mainly, and depends on the continuous activity of the *vasomotor centre*. This centre is situated in the floor of the fourth ventricle at the apex of the calamus scriptorius. It gives rise to fibres which pass down the cervical cord (possibly in the white matter of the lateral columns) to all the thoracic and the upper two lumbar segments, to end in the connector cells of the sympathetic which lie in the lateral horn of grey matter. The vaso-constrictor fibres then pass out in the sympathetic nervous system (as already described in detail, pp. 120–122) to the various parts of the body.

When the medulla oblongata is trans-sected at the level of the calamus scriptorius, a maximal fall of pressure occurs down to 30 to 40 mm. Hg, because the tonic impulses of the vasomotor centre are cut off. Section of the cord above the level of the first thoracic segment produces an equal depression of the blood pressure, as all the vasomotor fibres are still within the substance of the cord. Section below L2 produces a minimal effect, because all the vasomotor fibres have already passed out.

After division of the cord, the blood pressure recovers later owing to the

connector cells in the cord functioning independently as subsidiary vasomotor centres.

Stimulation of the anterior nerve roots between Th1 and L2 constricts the vessels in the corresponding segments of the body. Division of the sympathetic supply to a part results in loss of tone in the vessels. After a time a certain amount of recovery occurs, as the smooth muscle of the vessels is to a certain extent capable of postural activity independently of the nervous system.

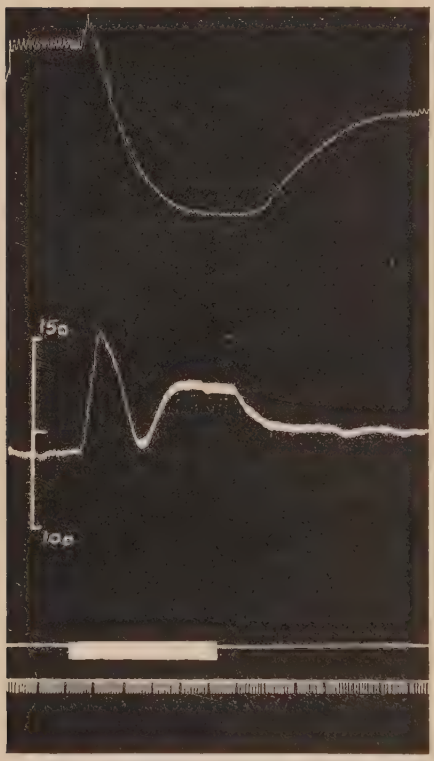

FIG. 87.—Effects of Stimulation of the Peripheral End of the cut Splanchnic Nerve. —VINCENT and WRIGHT.

Cat; upper tracing, volume of intestinal wall; lower tracing, blood pressure; signal, stimulation of splanchnic nerve. Time, in seconds. 100, 150, marked on vertical line = level of blood pressure in mm Hg. Adrenal veins open. Note the initial rise of B.P. followed by a transient fall ("dip") and again by a rise. Intestinal volume diminishes throughout period of stimulation (except for transient initial dilatation).

The activity of the vasomotor centre cannot be studied solely by recording the general blood pressure. A rise in blood pressure may be due to increased peripheral resistance or to increased cardiac output; if the peripheral resistance is halved and the cardiac output doubled, the blood pressure remains unchanged. Changes in the calibre of the vessels in the various organs may be investigated by enclosing the kidney, limb, etc., in a suitably shaped air-tight box (*plethysmograph, oncometer*) which is connected with a Marey's tambour or piston recorder. An increase in the volume of the organ signifies vaso-dilatation, and vaso-constriction is accompanied by shrinkage of the organ.

Stimulation of the peripheral end of the cut splanchnic nerve produces a marked rise of blood pressure and constriction of the vessels of the viscera as shown by oncometer records, and secretion of adrenaline by the medulla of the gland. The blood pressure curve is usually complex owing to the variable effects which may be produced by small doses of adrenaline: (i) in anæsthetized animals (especially under ether) and if the initial B.P. is high, adrenaline in small amounts lowers the B.P., producing a transient fall or "dip" in the tracing (Fig. 87). This dip is abolished by tying the adrenal veins or by division of the sympathetic fibres passing to the gland (Vincent and Wright).[1] (ii) In the decerebrate

[1] Vincent and Wright, *Quart. J. Exp. Physiol.*, 1924, vol. xiv, p. 285.

animal after the anæsthetic has been blown off, and especially if the initial B.P. is low, the small amount of adrenaline produces a secondary *rise* of B.P., which too is abolished by exclusion of the adrenals (Vincent and Curtis).[1]

Functions of Vasomotor Centre.—i. The respiratory centre adjusts the pulmonary ventilation according to the varying needs of the body; the vasomotor centre, on the other hand, endeavours to maintain a *steady level of blood pressure* under most normal conditions; any rise of blood pressure at rest inhibits the vasomotor centre, relaxes the peripheral arterioles, and so restores the blood pressure to its normal level. This has been shown by the cross circulation experiments of Anrep and Starling. The head of a dog A is perfused with blood from a heart-lung preparation. If the pressure in the cerebral vessels of A is artificially raised, the vasomotor centre is inhibited as proved by a fall of general blood pressure in A; conversely if the pressure in cerebral vessels of A is lowered the centre is stimulated as shown by a rise of general blood pressure in this animal. This mechanism ensures an adequate blood supply to the brain. If an animal is placed with its back in the vertical position and the feet down, the blood pressure momentarily falls owing to the effect of gravity. This produces a diminished blood supply to the brain. The vasomotor centre is stimulated and the blood pressure rises rapidly to normal (from constriction of splanchnic area), or may go higher still (L. Hill). Similar results are obtained in man in passing from the horizontal to the erect position.

In a person who is weakened by illness or who has been in bed for a long time, vasomotor compensation is feeble and giddiness or fainting may result on standing up, from anæmia of the brain.

In patients who are anæsthetized to a surgical degree, the abdominal wall is toneless and the vasomotor centre is depressed. Carelessly raising the upper part of the body may thus prove dangerous.

ii. The main vaso-constrictor fibres pass to the vessels of the splanchnic area and skin; very few fibres, and those of little functional importance, can be traced to the vessels of the brain, heart, lungs, or skeletal muscle, etc. The vasomotor mechanism is thus able to *redistribute* the blood, *i.e.* drive it out of the less important regions and send it to the parts which need it most, according to their requirements.

iii. The vasomotor mechanism helps to overcome the influence of *gravity*. Gravity tends to cause the blood to accumulate in the lower limbs and the splanchnic area. This is overcome (i) partly by the vasomotor centre, which constricts the vessels in the dependent parts, diminishes their capacity to hold blood, and thus makes the blood available for the other regions of the body, especially the brain. The vasomotor centre is stimulated (α) by the lowered pressure in the blood vessels supplying it, (β) by oxygen deprivation from reduced blood supply. (ii) By the suction action of the respiratory movements, the intermittent contraction of the skeletal muscles, and the tone of the abdominal wall, which aid the venous return to the heart. The importance of these factors is illustrated by L. Hill's experiments.

1. If the spinal *cord* is divided at Th1, there is, as stated, a marked fall of blood pressure and paralysis of the abdominal wall. If the animal is placed in the "feet down" position (*v. supra*) the blood pressure falls to zero.

[1] Vincent and Curtis, *Journ. Physiol.*, 1927, vol. lxiii. p. 151.

The blood passes through the dilated splanchnic vessels into the capacious abdominal veins, where it is retained under the influence of gravity, as the normal compressing action of the abdominal wall is lost.

2. If the *splanchnic* nerves are divided, the blood pressure falls, but the circulation may still remain adequate even in the "feet-down" position. A peculiar form of breathing develops in which powerful compression of the abdomen coincides with the inspiratory movement of the chest wall, and thus a maximum suction action is obtained. On dividing the abdominal wall by a crucial incision the pressure falls further. If the thorax is suddenly opened, the circulation ceases altogether.

The vasomotor centre can be influenced by the following factors :

1. Higher Centres.—(i) A rise of blood pressure commonly occurs in emotional stress and in anticipation of muscular exercise ; (ii) inhibition of the vasomotor centre may in part be responsible for the fainting fits of anæmic girls (p. 257).

2. Quality, Quantity, and Pressure of the Blood supplied to the Brain.—It can be shown that the CO_2 and *oxygen* content of the blood reaching the brain regulate the activity of the vasomotor centre.

i. Excessive ventilation of an animal's lungs with atmospheric air, so as to lower the CO_2 content of the blood, produces a considerable fall of blood pressure and relaxation of the blood vessels of the splanchnic area, as shown by increase in the volume of the viscera. The pressure can be restored and raised above normal by ventilating with air containing excess of CO_2 (Dale and Evans). Excess of CO_2 in the blood—*e.g.* in *asphyxia*—raises the blood pressure.

ii. (α) Breathing air containing too little oxygen stimulates the vasomotor centre and raises the blood pressure. Similarly the blood pressure rises in consequence of the oxygen lack occurring at high altitudes.

(β) As a result of cerebral tumour, abscess, or hæmorrhage, the intracranial pressure is raised, the cerebral veins and capillaries are compressed, and the blood-flow through the brain is interfered with; anæmia of the vasomotor centre results, and the blood pressure is raised to improve the cerebral circulation. This reaction is of great importance in cerebral hæmorrhage, which may be regarded as equivalent to a rapidly forming new-growth in the brain. The compensatory rise of blood pressure helps to maintain the blood-flow in the brain, but, of course, makes the bleeding from the ruptured vessel more profuse. This sets up a vicious circle of further rise of intracranial pressure, further rise of blood pressure and more bleeding. It might be thought the venesection would be useful by lowering the blood pressure and thus giving the leaking vessel a chance to be closed by clot. A moment's reflection shows that a fall of blood pressure would cause death from cerebral anæmia so long as the intracranial pressure remains high. The essential thing to do is to lower the intracranial pressure by lumbar puncture or by decompression, *i.e.* removal of part of the skull cap which allows the escape of blood or clot. A lower blood pressure is then sufficient to maintain an adequate cerebral circulation. As the blood pressure falls the bleeding may tend to diminish or cease.

iii. The blood pressure in the cerebral vessels (p. 281).

3. Reflexly from (i) *Heart.*—As already described (p. 257), the *depressor* nerve arises in the arch of the aorta and the wall of the left ventricle, and

passes up to the vasomotor centre. It inhibits the centre and causes relaxation of the splanchnic vessels. The depressor nerve acts as a safety valve mechanism which prevents excessive rise of the blood pressure at rest. It may also come into action during the height of systole to produce momentary relaxation of the arterioles and to allow the blood to leak out more readily into the capillary bed (p. 258). *Pressor* fibres are also present in the vagus: stimulation of the central end of the vagus may reflexly produce a pure rise of blood pressure, or an initial rise followed by the more usual fall. These pressor fibres may stimulate the vasomotor centre when the blood pressure is low, *e.g.* as a result of hæmorrhage (p. 181).

(ii) *Other Regions.*—Stimulation of the central end of a large nerve like the great sciatic produces effects which depend on the strength and nature of the stimulus. Strong, rapidly interrupted currents reflexly *raise* the blood pressure; weak or slowly interrupted currents produce a *fall*. Through a certain range of stimuli, the greater the strength of stimulus the greater the rise of pressure. Stimulation of the skin, muscles, or intestine, produces complex effects: afferent nervous impulses are set up which tend to lower the blood pressure, but this result may be masked by the liberation of a *pressor* substance in the injured tissue.[1]

Lovén Reflex.—If the central end of a small sensory nerve is stimulated to produce a rise of blood pressure, it may be found that the vessels generally are constricted, but the vessels of the part (*e.g.* limb) from which the sensory impulses came are relaxed. This is a form of reciprocal innervation by means of which an active organ may, by nervous reflexes, provide itself with a better blood supply at the expense of the rest of the body.

Rôle of Ductless Glands.—There is no reliable evidence that the adrenal medulla is responsible or necessary for the maintenance of normal vasomotor tone at rest. During exertion adrenaline is secreted and helps to redistribute the blood to the active parts (cf. p. 128). There is no evidence that the pituitary body regulates arteriolar tone, though it is believed to be responsible for the tone of the capillaries (cf. p. 149).

All tissue extracts (apart from "pituitrin" and adrenaline) lower the blood pressure on intravenous injection.[2] The active principle is perhaps a mixture of *choline* and *histamine* (Dale). Choline stimulates the vagus and slows the heart, and histamine dilates the capillaries (p. 290). Tissue extracts (particularly extracts of liver) and histamine-choline mixtures have been given subcutaneously to patients with high blood pressure. The pressure is lowered to some extent but the effect is very transient, only persisting for a few hours.

Influence of Respiration.—1. During *inspiration*, the negative pressure in the thorax is increased. This pulls on the walls of the thin capillaries and venules which surround the alveoli of the lung and increases the lumen of these vessels. One-eighteenth of the blood volume can be accommodated in the pulmonary bed during expiration, and one-twelfth during inspiration (Starling). Some of the blood which is expelled by the right heart is held up

[1] Vincent and Thompson, *Journ. Physiol.*, 1928, vol. lxv. p. 327. It appears from this work that under certain conditions *pressor* (as well as depressor) substances may be liberated from injured tissues. It has similarly been found that tissue extracts may *at times* raise the blood pressure.

[2] See footnote 1.

in the lungs to fill the dilated vessels, and less therefore reaches the left heart. The left ventricular output consequently falls and the systemic blood pressure is lowered. During *expiration* the intrathoracic negative pressure is diminished; the result is that some of the excess blood is squeezed out from the pulmonary bed. The left heart receives this blood in addition to the output of the right heart, and so the blood pressure rises.

2. The inspiratory descent of the diaphragm and the increased negative pressure in the thorax increase the venous return to the heart; in some subjects the rate of the heart is increased during inspiration and slowed during expiration. These factors operating alone tend to raise the blood pressure during inspiration and lower it during expiration; but, as shown above the varying capacity of the pulmonary bed lowers the blood pressure in inspiration and raises it during expiration. In man, the total effect of respiration on the blood pressure is negligible (Wiggers). In anæsthetized animals as a rule a regular variation of blood pressure with respiration is noted. The rise occurs *after* the beginning of inspiration and the fall *after* the onset of expiration.[1]

The resistance in the pulmonary bed is slight, for, as stated, the vasomotor supply to the pulmonary arterioles is not important. The pressure in the pulmonary artery is 43 to 30 mm. Hg systolic, 20 to 12 mm. Hg diastolic. The pulmonary pressure rises during expiration and falls during inspiration.

Over-distension of the alveoli (*e.g.* in emphysema) tends to compress and obstruct the vessels lying in their walls, and thus increases the resistance in the pulmonary bed and puts a greater load on the right heart.

In mitral regurgitation or stenosis some blood is retained in the left auricle and the rest is accommodated in the distensible pulmonary veins (p. 266), but if the right ventricle is in good condition there is little interference with the emptying of the right heart.

Local Action of Metabolites.—It is found that the blood vessels supplying an active organ become greatly dilated, so that a greater quantity of blood reaches the active tissue each minute. It is believed that certain products liberated during activity cause local relaxation of the arterioles. The nature of these *metabolites*, as they are called, is not known for certain, but may be CO_2 or lactic acid (Gaskell).[2] It should be noted that when these products of tissue activity pass into the general circulation they stimulate the vasomotor centre, produce general vaso-constriction, and cause the blood to be driven under increased pressure to the active organs, the blood vessels of which have already been relaxed to accommodate this increased blood-flow. Each tissue, in a sense, can regulate its blood supply in accordance with its needs.

Vaso-Dilatation.—The main facts will be briefly summarized:

A *depressor point* is described 3 mm. behind the vasomotor centre, which, when stimulated, gives rise to a fall of blood pressure. It is doubtful whether this point can be regarded as a separate vaso-dilator centre; it is more probably a region where *afferent depressor* fibres which are passing to the vasomotor centre are situated superficially. Vaso-dilator fibres are found as follows:

[1] *i.e.* in each case the pulmonary bed factor comes into operation before the change in venous return.

[2] Or possibly a "histamine-like" substance (p. 292).

1. Posterior nerve roots (see p. 34).

2. Cranial and sacral autonomic—*i.e.* chorda tympani (p. 124), palatine nerves (p. 124), nervi erigentes (p. 119).

3. Sympathetic nervous system : (i) if the anterior nerve root of Th12 is stimulated by slow induction shocks, dilatation of the vessels of the kidney occurs ; (ii) after the injection of *ergotoxin*, which paralyses the vaso-constrictor fibres of the sympathetic system, it is found that doses of adrenaline which were previously pressor now lower the blood pressure ; (iii) if the peripheral end of the cut right splanchnic nerve is stimulated at short intervals, a fall of blood pressure is obtained instead of a rise (Thompson). These experiments show clearly that a number of dilator fibres are intermingled with the more numerous vaso-constrictor fibres of the sympathetic.

4. In the peripheral nerves : (i) vaso-dilatation results if the freshly divided sciatic nerve is stimulated peripherally by slow induction shocks ; (ii) if three days are allowed to elapse after the section, the vaso-constrictor fibres degenerate, but the vaso-dilators still persist, and so stimulation of peripheral end of the nerve results in vaso-dilatation.

General vaso-dilatation usually results mainly from inhibition of the vaso-constrictor centre, *e.g. via* the depressor nerve or afferent visceral or somatic nerves, or by a rise of blood pressure (p. 281). Local dilatation of the skin arterioles is produced by a number of agencies which act by liberating histamine in the part (p. 294 *et seq.*). The chemical products of metabolism relax the vessels of an active tissue.

Measurement of Blood Pressure.—In *animals* the blood pressure can be recorded graphically by inserting a cannula into the carotid artery and connecting it with a mercurial manometer provided with a float and writing-point which records on a moving smoked surface. The cannula and tubing are filled with an anti-coagulant fluid, *e.g.* half saturated sodium sulphate solution.

In *man* the upper arm is encircled with a rubber bag (enclosed in an unyielding cuff) which is connected to a pressure pump and a manometer. The pressure in the bag is rapidly raised to 200 mm. Hg to obliterate the brachial artery and to overcome any spasm which may be present. The pressure is then lowered until the pulse can just be detected at the wrist. This is the measure of the systolic pressure.

Auscultatory Method.—If a stethoscope is placed over the brachial artery below the cuff, a series of sounds are heard as the pressure on the artery is diminished (Korotkov).

First phase : the sudden appearance of a clear sound which lasts while the pressure is lowered by about 14 mm. Hg. The *first* appearance of this sound is the criterion of systolic blood pressure.

Second phase : the sound becomes murmurish in character, and can be heard while the pressure is lowered by another 20 mm. Hg.

Third phase : the murmur is replaced by a sound which becomes progressively louder and more " banging " in character, during the next 25 mm. of fall of pressure.

Fourth phase : the sound suddenly becomes soft and muffled. The point at which the sound *begins to fade* is usually taken as the criterion of the diastolic pressure.

Fifth phase : disappearance of all sound. (This has been regarded by

some workers as the diastolic point.) In many cases, however, total disappearance of the sound does not occur.

Normal Blood Pressure.—In childhood the systolic pressure gradually increases. It ranges from 75 to 90 mm. during infancy, from 90 to 110 mm. in childhood, and 100 to 120 mm. about puberty. The diastolic pressure ranges round 50 mm. during the first few years of life, and after that until puberty remains fairly constant at 60 mm.

In adults the average normal systolic pressure is 125 to 130 mm. with a range of ± 15, *i.e.* figures between 110 and 145 mm. are well within the range of the normal. In old people it is between 140 and 150 mm. It may be 5 to 10 mm. lower in women than in men. The maximum pressure at the height of ventricular systole is called the systolic pressure; the minimum pressure during diastole is the diastolic pressure. The difference between the two is the pulse pressure.

The *systolic pressure* fluctuates with physiological conditions of exertion, mental state, sleep, meals, etc. For comparison, readings in the recumbent position, with the artery at heart level, are employed.

The *diastolic pressure* is a measure of the peripheral resistance, and depends mainly on the tone of the arterioles. It is less subject to temporary fluctuations than is the systolic pressure. It is normally 35 to 50 mm. lower than the systolic pressure.

The *pulse pressure* is the rise of pressure produced by ventricular systole. Though there is a general correspondence between the size of the pulse pressure and the output of the heart in the sense that both increase or decrease synchronously, there are no definite quantitative relations between the two. The same pulse pressure may at different times and in different individuals correspond to systolic discharges of very different volumes. At any age a systolic blood pressure which is persistently over 150 mm., as shown by repeated observations, a diastolic pressure constantly over 100 mm., or a pulse pressure constantly over 50 mm. is abnormal. One may arbitrarily place the lower limit of normal systolic pressure at about 105 mm. Hg.

Hypertension.—Hypertension may occur as a more or less temporary condition in association with eclampsia, uræmia (p. 474), asphyxia (p. 282), raised intracranial pressure from any cause (p. 282), nervous disturbances such as severe pain or great emotion (p. 282).

Persistent arterial hypertension cannot yet be satisfactorily accounted for.

1. It occurs in association with chronic *renal disease* (chronic interstitial nephritis). The renal vessels are narrowed and many glomeruli are obliterated in this condition. Cohnheim regarded the hypertension as a physiological reaction which increases the pressure in the remaining glomeruli and thus favours the elimination of soluble waste substances from the body. It has been suggested that when the kidneys are not functioning effectively, toxic bodies are retained or abnormal products of metabolism appear which act directly on the vasomotor centre and produce a rise of blood pressure.

2. *Hyperpiesia* or essential hypertension is a condition in which a persistent raised blood pressure is present without gross pathological changes in the kidneys or in the arteries. According to Geoffrey Evans the hypertension is usually due to narrowing of the small arteries of the splanchnic area owing to intimal proliferation ("*diffuse hyperplastic sclerosis*"). If the renal vessels escape, no albumin may be present in the urine. Some cases

may possibly be due to a disorder of the *vasomotor centre* which no longer maintains the normal range of blood pressure, but produces excessive arterial tone and hypertension.

Dawson found in 8 per cent of 650 school children examined that the systolic blood pressure was definitely above the normal limits for their age, *i.e.* it exceeded 130 mm. Hg. In two classes which were working for the Oxford Senior examination the incidence of hypertension was two and a half times as great as in the school as a whole. These observations are of great interest, for they show: (i) that hypertension may set in at an early age; (ii) that predisposed subjects may respond excessively to emotional or other stimuli, and it is possible that the vaso-constriction thus produced may persist after the exciting stimuli have been removed. There is no doubt, too, that hypertension tends to run in families.

Aortic Disease (see p. 267).

HYPOTENSION is a symptom observed in the following conditions: (i) shock (p. 298); (ii) disorders of internal secretions, especially Addison's disease (p. 133); (iii) in certain cases of heart failure; it should be noted, however, that in the early stages of heart failure the blood pressure may be kept within normal limits by the compensatory action of the vasomotor mechanism; the presence of a normal blood pressure does not exclude the possibility that the heart is beginning to fail; (iv) cachexia from tuberculosis, cancer, anæmia; (v) nervous disorders such as neurasthenia.

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VENOUS PRESSURE

To estimate the venous pressure in man two main methods—the indirect and the direct—have been employed. The *indirect* methods consist in determining the external pressure necessary to produce collapse of a small superficial vein, or the pressure which just prevents refilling of a vein previously emptied by "milking" towards the heart. The *direct* methods consist in placing a manometer in communication with a vein by means of rubber tubing and a hollow needle of adequate bore. The vein usually chosen is the median basilic, at the bend of the elbow.

The needle and tubing are sterilized in liquid paraffin, which retards coagulation of the blood. An aneroid manometer (Claude) is employed graduated in centimetres of water. The patient lies on a couch with the arm horizontal from the shoulder and the elbow supported on a suitable block. The position of the vein is then 6 to 8 cm. below the level of the sternum at the angle of Louis. The muscles of the arm must be completely relaxed.

Fifty per cent. of normal subjects give readings of 5 to 10 cm. H_2O and

90 per cent. between 5 to 15 cm. H_2O (Bedford and Wright). Different observers have placed the arm in different positions and have taken various points on the chest wall as criteria of heart level. Moritz and Tabora, for example, adjusted their readings to the level of the right auricle, which they take as being 5 cm. behind the front of the sternum at the fourth costal cartilage. Bearing these facts in mind the figures obtained for the venous pressure agree fairly well with those obtained by Krogh for the capillaries (p. 293). The blood pressure falls steeply in its passage through the arterioles. The gradient between the capillaries and veins is very slight.

Venous pressure is dependent on capillary rather than arterial pressure; capillary pressure is regulated to some extent by the condition of the arterioles. If the arterioles are dilated by means of an inhalation of amyl nitrite the venous pressure rises definitely by several cm. H_2O, the rise running approximately parallel to the increase in pulse-rate.

The venous pressure is raised by muscular *exercise*. Readings taken immediately after exercise vary from 9·5 to 19·5 cm. H_2O, and in all cases a definite fall is observed after a few minutes' rest, the average fall being 5 cm. This rise of pressure may be due to raised intra-auricular pressure resulting from increased venous return, or to arteriolar relaxation in the active muscles producing a raised capillary pressure, or to a combination of these two factors.

Effect of Respiration.—In normal persons respiratory variations in pressure are not observed in the arm veins. In a pathological case where the venous pressure was 30 cm. H_2O, oscillations of $\frac{1}{2}$ to 1 cm. were noted. Excessive pulmonary ventilation in normal subjects lowers the venous pressure by 1 to 3 cm. H_2O. If the intrathoracic pressure is raised by the subject taking a deep inspiration and holding it for as long as possible, a considerable rise in venous pressure can be produced, the degree of rise depending on the depth of the inspiration and the duration of the apnœa, *e.g.* a rise from 7 cm. to 25 cm. H_2O may be obtained (Bedford and Wright). When considerable venous engorgement is present, it can be easily appreciated clinically by observing enlargement of the liver and distension of the cervical veins. Unless a rise in venous pressure occurs before clinical evidence of venous engorgement is manifest, the determination of venous pressure in cases of heart disease will be of little practical importance. According to Bedford and Wright the venous pressure in pathological cases is not raised unless obvious signs of heart failure are present. French workers, however, maintain that a rise in venous pressure may be the first indication of incipient heart failure. When marked congestive failure is present the venous pressure in the arm veins is undoubtedly raised, *e.g.* to 30 or 35 cms. H_2O. It falls as the clinical condition improves.

REFERENCE

Bedford and Wright.—*Lancet*, 1924, vol. ii. p. 106.

THE CAPILLARIES

Structure.—The capillaries are lined by thin, flattened, polygonal cells which contain a definite nucleus and are joined together by cement substance.

Branched *cells of Rouget* are present at intervals outside the capillary wall. They can be demonstrated by vital staining with methylene-blue. The cells appear to be elongated in the length of the capillary, and branches pass transversely round the vessel ; a fibrillar appearance can be noted in the protoplasm. These Rouget cells are probably modified muscle cells [1] which regulate the size of the capillaries ; transitional forms can be detected between them and the circular plain muscle fibres of the walls of the arterioles. The muscle coat has become modified in the case of the capillaries to leave much of the endothelial surface uncovered, and so permit the passage of various substances to and from the tissue spaces with a minimum of resistance. These cells possess tone or posture, as does the arteriolar wall. This tone varies with *nervous*, *hormonal*, and other influences, and the diameter of the capillary at any moment can thus be controlled.

Independent Contractility of the Capillaries. — The capillaries are capable of altering their calibre independently of the state of the arterioles or venules. If their tone is high they can resist the distending force of a raised venous or arteriolar pressure ; if their tone is low they tend to follow passively changes in the arteries and veins.

1. Direct Observation.—In the web of the frog's foot it may be noted that when the arteries contract the capillaries may dilate and the number of visible capillaries may increase three- or four-fold. Urethane, applied to the frog's tongue, dilates the capillaries without affecting the arterioles. Further, should the capillaries be contracted firmly it is very difficult to force them open by raising either the arterial or the venous pressure. If the capillaries are relaxed, however, by light mechanical stimulation, they fill readily from either end (Krogh).

By means of the skin microscope (Müller, Weiss) the capillaries of the human skin can be studied at the root of the nail. This site is chosen because here the capillaries run parallel to the surface, and a considerable length of loop may be examined. By means of cedar-wood oil the surface layers of the epidermis are made transparent. If a light is then shone on the skin, the capillaries are readily seen and can be examined with the low powers of the microscope. A series of adjacent vessels may show alterations in their calibre from moment to moment. The rate of flow as judged by the velocity of the corpuscles also seems to be constantly changing.

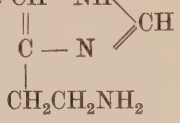
2. Indirect Evidence (see also pp. 290 and 294).—The *colour* of the skin depends on the calibre of the surface *capillaries*, and of the subpapillary venous plexuses ("*minute vessels*") ; if they are dilated and a considerable blood flow takes place through them, the colour is red ; if the blood stagnates in relaxed capillaries, its oxyhæmoglobin undergoes extensive reduction, and so the skin is blue ; if the capillaries are contracted, the skin is pale. The *temperature* of the skin, like that of any part, depends on the *amount* of blood flowing through the part, which in turn depends on the calibre of the *arterioles*. The capillaries thus regulate the amount of blood which is present *in* a part at any moment, and the arterioles the amount passing *through* the region during any given period. A warm pale skin must mean dilated arterioles and con-

[1] Clark, however, regards the Rouget cells as modified connective tissue cells and denies that they are contractile ; he describes independent movements of the endothelial lining which may carry the Rouget cells with them or leave a space between the capillary lining and the Rouget cells (*Amer. Journ. Anat.*, 1925, vol. xxxv., pp. 239, 269).

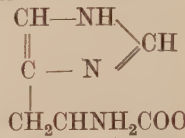
stricted capillaries. A cold blue skin means constricted arteries and dilated capillaries (Ebbecke). It is obvious that the capillaries are not merely passive agents. A warm red skin indicates that both the arterioles and the capillaries are relaxed.

Action of Histamine.—It will be convenient to consider at this point the pharmacological action of histamine.

Histamine is β-Iminazol Ethylamine



It is formed by the removal of CO_2 from histidine



(Iminazol α amino-propionic acid which is an amino-acid present in proteins).

Histamine has been definitely extracted from the mucous membrane of the gut, liver, lung, and the posterior lobe of the pituitary body. It is probably present in extracts of most of the tissues of the body and largely accounts for the blood pressure lowering action shown by these extracts (cf. pp. 283 and 147). It has a powerful secretagogue action. causing in animals an increased flow of saliva, tears, gastric and pancreatic juice ; in man, however, its action is limited mainly to the *gastric* glands (cf. 387). It is a stimulant to smooth muscle, *e.g.* of the intestinal wall, uterus, and bronchioles, and in some animals (guinea-pig) causes death from bronchial spasm which prevents effective pulmonary ventilation. In the cat, when histamine, even in minute doses (1 to 2 mgrm. per kg. of body weight), is injected intravenously, it causes a marked fall of blood pressure, although it constricts the arterioles as shown by the fact that it causes contraction of isolated strips of artery suspended in warm saline. A purely arterial system can be prepared by cutting the mesentery at its attachment to the intestine. The superior mesenteric artery and its branches are then perfused, and it is found that histamine diminishes the rate of escape of fluid by constricting the arterioles. If the heart is examined in an animal poisoned with histamine, it is found to be beating forcibly, but its cavities are empty and the output is very small. There has been a failure in the venous return, which is due to *capillary paralysis* produced by histamine. This can be proved as follows. The nerves going to the limb of a cat are severed. The arterioles consequently relax, and the limb becomes warm owing to the larger blood-flow through it. The pad of the foot remains pale, indicating that the capillaries are contracted in spite of arteriolar dilatation (*v. supra*). Injection of acetyl-choline (which is a pure arteriole dilator) does not alter the colour of the pad, because the arterioles were full before. Histamine, on the other hand, at once makes the pad flush because it paralyses the capillary wall, which now gives way before the arteriolar pressure. If a histamine solution is dabbed on to an organ like the pancreas it is seen to become flushed with blood. As the arterioles are contracted the increased vascular content of the organ must be attributed to capillary dilatation.

The profound depressor action of histamine shows how serious are the effects on the circulation of loss of capillary tone. Krogh has shown that, compared with the number of capillaries present in a muscle, the number which normally contain blood is very small. If Indian ink is injected into the vessels of a resting muscle, very few capillaries can be seen on examination, and most of these are very narrow. If the experiment is repeated in the case of a tetanized muscle, 40 to 80 times as many capillaries are visible in any unit area, and they are all widely dilated. Now capillaries contain no valves, so if blood comes to a part, it must first fill the capillaries before it can pass on into the veins. Once it reaches the veins, its return to the heart is relatively easy. The contractions of the skeletal muscles drive the blood on, and it cannot pass back owing to the presence of the valves. In the capillaries, however, muscular activity merely squeezes the blood from one capillary to another, only to return in the intervals between the contractions. Normal capillary tone is thus of extreme importance. In muscular exercise the muscular capillaries, it is true, relax, and can retain a great deal more blood, but then the blood-flow to the muscles is greatly increased by diminishing the lumen of the arterioles in other regions of the body. If the capillaries all over the body relax as after the injection of histamine, they can retain so much blood within them that after they are filled very little blood is left to reach the veins. The venous return falls, the output of the heart diminishes, and the brain and tissues generally suffer severely from oxygen lack owing to their impaired blood supply.

Histamine also increases the permeability of the capillaries (p. 295) so that much fluid escapes from the vessels into the tissue spaces, thus still further reducing the volume of circulating fluid. The red blood count per c.mm. and the hæmoglobin percentage are consequently found to rise. The increased *viscosity* of the blood which results throws a further load on the circulation because greater frictional resistance is encountered in the narrow arterioles. Dale has shown that the anæsthetics (chloroform, ether) sensitize the capillaries to the action of histamine, so that in unanæsthetized animals about ten times the dose of the drug is needed to produce an equivalent depression of blood pressure. Œdema of the tissues is not very evident in histamine poisoning for this reason : œdema that can be demonstrated by pitting on pressure does not occur until the volume of a tissue has increased by about 10 per cent. If the whole blood plasma were to pass into and become *uniformly* distributed throughout the tissue spaces, pitting could not be demonstrated, for there is not enough fluid present in the circulation to produce the requisite degree of œdema.[1]

Following the initial fall of pressure produced by small injections of histamine, the pressure may rise *above* the normal level ; this after-rise is due to a compensatory secretion of adrenaline, for it is abolished by extirpation of the adrenal glands (Burn and Dale).[2]

In the dog, monkey, and man histamine produces *arteriolar dilatation* in addition to capillary paralysis. A subcutaneous injection in man of 0·3 mgrm. histamine causes general flushing of the skin, a rise in its temperature of 1° or 2° C., a small decline of systolic, a great fall of diastolic pressure and an appreciable rise of pulse rate ; the flush is most conspicuous in those parts

[1] Drury and Jones, *Heart*, 1927, vol. xiv. p. 55.
[2] Burn and Dale, *Journ. Physiol.*, 1926, vol. lxi. p. 185.

that are previously red. Even doses of 0·06 mgrm. cause flushing of the skin of the face and a rise of 0·5° C. in its temperature [1] (cf. p. 297).

Nerve Supply.—1. It is probable that *sympathetic fibres* pass to the Rouget cells of the capillary wall. In the frog capillary constriction may follow sympathetic stimulation even after the heart has been removed, thus eliminating passive effects. Stimulation of the peripheral end of the cervical sympathetic causes contraction of the capillaries of the rabbit's ear even after the arterioles have been obstructed and the circulation thus brought to a standstill. Tonic impulses may pass along the sympathetic; extirpation of the sympathetic ganglia leaves the corresponding capillaries in a dilated condition for a prolonged period, tone recovering slowly after about 100 days (Krogh).

2. Stimulation of the peripheral end of a cut posterior nerve root produces dilatation of the capillaries (and arterioles) of the corresponding skin segments. According to Lewis (p. 34) this vaso-dilatation is produced *indirectly* by the release of a histamine-like substance locally which then gives rise to the vascular changes.

Hormone Control.—1. Removal of the *pituitary* body in the frog leads to the development of cutaneous œdema. The capillaries are found to dilate strongly a few hours after the extirpation has been carried out. After one or two weeks the capillaries regain their powers of contracting, but their behaviour is still somewhat irregular. Periods of extreme contraction alternate with a state of maximal dilatation. Perfusion of the vessels of the web of the foot with a very dilute solution of pituitrin, *i.e.* extracts of the posterior lobe of the pituitary body, does not affect the arteries, but produces strong contraction of the capillaries. These experiments suggest strongly that in the frog, at any rate, capillary tone depends largely on the secretion of the pituitary body. No such convincing evidence is available in the case of the human subject. Certain conditions of solid œdema (*Milroy's disease*) are said to be associated with alterations in the sella turcica and other evidence of pituitary dysfunction. In *shock*, in which capillary paralysis is probably present, pituitrin may help to raise the blood pressure and improve the general condition by constricting the capillaries and so increasing the venous return to the heart. Pituitrin injected subcutaneously in man constricts the local capillaries and produces a circumscribed pale area; if injected intramuscularly, general pallor of the skin results (cf. pp. 147, 149).

2. Metabolic products formed during activity have a dilator effect on the capillaries (and arterioles), as has already been noted in the case of active skeletal muscle. It is not probable that this is due to the acid properties of these metabolites. Experiments have shown that increasing the hydrogen ion concentration many hundreds of times above that found in blood will dilate the capillaries, but the increase of cH which takes place in active tissues is very slight indeed, and such alterations do not produce any dilator effects experimentally. Lewis suggests that histamine may be the agent concerned.

We have seen that contracted capillaries are a necessity in the case of resting tissues in order that the blood may circulate freely and the venous return be adequate. According to Krogh the same capillaries in any area are not contracted continuously; first one group of capillaries relaxes and then another, and thus the blood comes in contact with different parts of the

[1] Harmer and Harris, *Heart*, 1926, vol. xiii. p. 381.

tissue and an even state of nutrition is maintained. This may be true of certain parts of the body, *e.g.* the glomeruli of the kidney (p. 461); but it does not appear to apply to the case of human skin. According to Lewis,[1] under normal conditions the majority of the capillaries in the skin are open and their tone is relatively *stable* and unfluctuating.

Capillary Blood Pressure.—The older methods gave readings for the skin capillaries of 100 to 750 mm. H_2O pressure, but the technique employed has been severely criticized.

Krogh's method is as follows. A narrow piece of glass tubing is drawn out to a fine point and filled with saline. The skin capillaries are directly inspected, a suitable loop is found and pierced, and the tube is left in for a few seconds. The tube is previously connected with a hand bulb and a water manometer, and the pressure within it raised and read off on the manometer. If the pressure in the capillary is higher than in the glass tube, blood runs into the saline and *vice versa*. The pressure is then raised or lowered in the tube and tested on other capillary loops. In this manner very accurate readings can be obtained.

The capillary pressure varies with the vertical position of the point relative to the thoracic cavity. From a level of 7 cm. below the clavicle and upwards constant readings are obtained, the figures in different subjects being between 4·5 and 7·5 cm. H_2O. This is difficult to explain. Although there is a negative pressure in the thorax, a negative pressure is not found in the extrathoracic veins, because they are not rigid tubes and yield to the slightest pressure from outside. As the arm is raised the veins tend to collapse more and more. Though the internal pressure falls, this is made up by the increased frictional resistance to the flow of blood along them. The pressure in the capillaries thus remains constant.

Below heart level, the capillary pressure increases with the vertical distance. The full hydrostatic pressure is not realized, however; *e.g.* at 19 cm. below heart level the pressure was 17 cm., at 36 cm. it was only 32 cm. This is due to the presence of the valves in the veins and the pumping action of the muscles, which tend to keep the veins emptied and prevent the full hydrostatic pressure from being transmitted. If the arm is allowed to hang limply, the capillary pressure becomes very high, and swelling of the hands may occur from exudation of the fluid from the vessels by a process of filtration.

Still less is known about capillary pressure in internal organs. In the glomeruli of the kidney (p. 462) it is said that the pressure in the tufts may be little lower than the general arterial blood pressure. In the intestinal capillaries it must be higher than the pressure in the portal vein, which is about 10 mm. Hg (13 cm. H_2O). In the liver capillaries it may be very low indeed.

Vascular Responses of the Skin.—1. If the skin, for example on the front of the abdomen, is stroked quite lightly, a white line appears which is exactly limited to the area of skin stimulated, and is quite sharply outlined. The line appears after a definite latent period, persists for a minute or two, and then gradually fades. Sergent suggested that this response was indicative of adrenal insufficiency, and dignified it with the title of "la ligne blanche surrenale."

[1] Lewis, *Heart*, 1926, vol. xiii. p. 1.

Wright[1] has shown that this "white line" occurs in a large proportion of normal subjects and is not related to low systolic or diastolic pressure. It can be readily shown too that the white line is due to local *capillary* constriction.[2] (i) Each arteriole supplies an irregular area of skin, so that the local anæmia which results from its contraction would similarly be irregular in outline and not follow strictly the line of the stroke as does the "ligne blanche." (ii) The white line can be easily obtained on the skin of the forearm. If the arm be raised to the horizontal and the pressure in an armlet is rapidly run up to 70 to 80 mm. above the blood pressure of the subject (*i.e.* to about 200 mm. Hg), it is found that the white line can still be obtained and that its time relations remain unchanged. The same holds true even if an interval of ten minutes is allowed to elapse after applying the armlet. If the circulation is normal, the result of blocking an arteriole is to empty the corresponding capillaries, because the blood previously contained within them flows on into the veins. The effect of compressing the arm in this experiment has been, however, to slow down or stop completely the flow in the vessels distal to the block. In such a system, constriction of the *arterioles* would drive blood out of them into the capillaries and dilate them still further, as their contents cannot pass on in the normal way, owing to the obstruction to the natural outflow from the veins. The blanching of the skin must therefore be due to the contraction of the *capillary* wall, which actively drives the blood out into the neighbouring veins. This view has been confirmed by *microscopic* examination of the skin vessels. If *adrenaline* or *pituitrin* is injected into the skin of an arm in which the circulation has been arrested, it also causes local blanching, proving that these drugs produce capillary contraction.[3]

The white line can be elicited after all the nerve fibres to the skin have degenerated, proving that it is a *local* response of the capillaries to external stimulation. The maximum pressure which the capillary wall can exert on its contents when it contracts is 40 to 60 mm. Hg. If the pressure in a cuff surrounding the arm is raised to this figure, the venous pressure soon rises to the same level; the capillary pressure must therefore be of a slightly higher order. If, under these conditions, adrenaline is injected into the skin it still causes blanching. If the capillaries are *first* constricted by adrenaline and the venous pressure is subsequently raised by obstructing the outflow of blood from the limb, it is found that they can then resist a distending force in the veins of 80 to 100 mm. Hg, *i.e.* the resistance of a closed capillary is greater than the maximum pressure which it can exert on its contents when it contracts.

2. In subjects with more sensitive skins, or if heavier stroking is employed, a *triple response* may be obtained (Lewis). (i) After a short latency a *red* line develops which is sharply defined; it is first bright red in colour, but gradually assumes a bluish tinge indicating that the blood is stagnant and its hæmoglobin therefore is undergoing excessive reduction. Using the criteria described above, the red line can be shown to be due to capillary dilatation; it also can be obtained after the local nerve supply has degenerated. Sometimes the red line is flanked by a white line on either side. The central red line is due to the heavy stimulus over the line of the stroke, the bordering white lines result from the weaker stimulus where only slight

[1] Wright, *Endocrin.*, 1922, vol. vi. p. 1100.
[2] Cotton, Slade, and Lewis, *Heart*, 1917, vol. vi. p. 227.
[3] Lewis, *ibid.*, 1924, vol. xi. p. 109.

stretching of the skin occurred. This response is identical with the "tache cérébrale," found so commonly in meningitis, but long recognized as having no diagnostic significance. (ii) After a further interval of 15 to 30 seconds, a widespread flush or *flare* appears in sensitive subjects. This can readily be shown to be primarily the result of arteriolar dilatation. The flare spreads for a variable distance from the area stimulated, is mottled in colour from alternating islets of hyperæmia and normal skin, and the edge is crenated, as would be expected from the manner in which the arterioles are distributed to the skin. The colour is red throughout and does not tend to become purple from oxygen deficiency, proving that rapid flow of blood is occurring. If, over such an area of flushing, a line of light pressure be drawn, a white line appears which replaces the erythema over an area strictly limited to the zone stimulated. We have here the characteristic line of capillary constriction, superimposed on an irregular hyperæmia due to dilatation of arterioles. The temperature of the skin over the flare rises by 0·5° to 2° C. as a result of the increased blood flow. If the upper arm is compressed till the skin of the distal part of the arm is cyanosed, it is found that heavy stroking will still elicit the flare which appears bright red against a dark background, owing to the oxygenated blood from the deeper arterioles being forced into the skin vessels. The flare depends on an *intact* nerve supply to the skin; it is abolished when the local nerve fibres have degenerated. It is still obtained if conduction in the sensory nerves leading from the part is blocked by an injection of novocain into the nerve trunk; the reaction is therefore not a reflex through the central nervous system, but probably results from a *local axon reflex* (cf. p. 35). (iii) In susceptible subjects a *wheal* develops on the site of the red line. It reaches its maximum height in about 5 minutes, and may project 1 to 2 mm. above the general surface of the skin. It is due to *increased permeability* of the minute vessels which permits the escape of fluid, closely resembling plasma in composition, into the tissue spaces. The fluid contains 4 or 5 per cent. protein and traces of fibrinogen, and clots on standing. The wheal gradually becomes paler as it increases in size owing to compression of the minute vessels. A marked arteriolar flush must be present if effective whealing is to occur, because a rich blood supply is needed to provide the necessary fluid. The wheal is not due primarily to increased intracapillary pressure, for if the arm is compressed to produce venous congestion the wheals formed are smaller owing to the diminished blood-flow, in spite of the fact that the capillary pressure is raised. If trypan blue is injected intravenously into a normal person it does not escape into the tissue spaces, but it does pass into a wheal while it is forming owing to increased capillary permeability.

Lewis has shown that if *histamine* (even in dilutions of 1 in 3000) is injected into the skin it produces a typical triple response: (i) local dilatation of the capillaries and venules by direct action; (ii) widespread dilatation of surrounding arterioles from a local axon reflex; (iii) local increased permeability of the walls of the minute vessels, increased exudation of fluid and wheal formation. If the skin is firmly stroked and simultaneously a histamine solution is inoculated, similar "triple responses" develop in both cases and they have exactly the same time relations as regards onset and disappearance. He has brought forward evidence to show that heavy stroking or injuries to the skin cause the liberation of substances locally with a histamine-like

action ("H"-substance), and this may be the explanation of the skin reactions described. The evidence for this view is as follows :

(i) A large number of agents can produce the triple response : pricking, scratching, freezing, or burning the skin, the passage of strong electric currents, the inoculation of irritants such as 5 per cent. HCl, 5 per cent. NaOH, 1 per cent. morphine, 2 per cent. atropine, cantharides, peptone ; fish extracts, flea and gnat bites in susceptible subjects ; alcoholic extracts of skin, liver, and lung. Many dissimilar agents—all of which injure the tissues—thus produce the same complex vascular response ; the simplest explanation of this uniformity of action is that they all liberate the same chemical substance in the skin, and it is the latter which sets up the triple response.

(ii) If histamine is punctured into the skin, a vivid flare develops as stated, which fades to a considerable extent after 10 minutes. The blood supply to

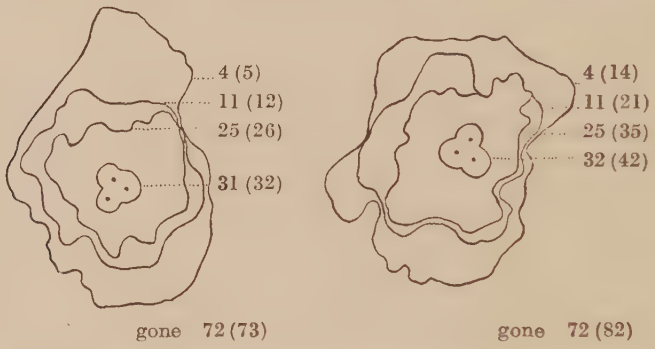


FIG. 88.—"Flare" response to injection of histamine in normal subject.

Left outline corresponds to left arm area, right outline to symmetrical right arm area of skin. The vessels of both arms were occluded. A group of three histamine punctures (1/3000) was put down on the right forearm 1 minute after occlusion, on the left forearm 10 minutes after occlusion. The circulatory arrest was continued in each case to the 11th minute, when both arms were released. The outlines of the flares aroused by the stimuli were outlined at the times noted in minutes in figures after release of vessels against the corresponding contours. Numbers in brackets represent corresponding times elapsing after stimuli were laid down (*e.g.* 4 (14) means outline 4 minutes after release of circulation and 14 minutes after puncture was performed). Position of punctures shown as dots. (Lewis, *Blood Vessels of Human Skin and their Responses.*)

one arm is obstructed, a histamine solution is inoculated, the occlusion of the vessels is kept up for 11 minutes and is then released. The control arm is similarly treated, except that the histamine is inoculated 1 minute before the vessels are released. Both arms now become red ("*reactive hyperæmia*") but this redness rapidly fades, except in the regions where the histamine was injected. As soon as the histamine flares are visible their outlines are marked out in ink, and again at suitable intervals as fading takes place (see Fig. 88).

It is found that the fading in the two arms occurs *simultaneously* : the conclusion is drawn that when histamine is injected into skin in which the circulation is arrested it is *retained* in the skin and produces its full effects as soon as the circulation is released. On the basis of these findings a crucial experiment can now be performed (Lewis). The observations described are repeated, but instead of inoculating histamine, the skin of a sensitive subject is firmly stroked ; exactly the same results are obtained, *i.e.* the flare develops and fades in the same way in both arms. Clearly the mechanical stimulus

itself does not reflexly produce the flare, because if that were the case during the 10 minutes of vascular occlusion which followed the application of the stimulus, these effects should have passed away. One must conclude that the mechanical stimulus causes the liberation of some chemical substance which is retained intact in the skin during the period of circulatory arrest and produces its effects as soon as the circulation is released (cf. p. 34).

The evidence so far given may be summarized thus: (i) a large number of agents which injure the tissues elicit the "triple response"; (ii) the "flare" response to heavy stroking develops in a normal manner after 10 minutes of circulatory arrest, suggesting that a chemical body acts as an intermediary; (iii) responses which are identical in all respects can be obtained by inoculating histamine in high dilution into the skin. There is little doubt therefore that some body with a histamine-like action ("H"-substance) is liberated when the skin is injured. That this "H"-substance is probably histamine itself is suggested by the following observations: (i) Histamine has been definitely demonstrated in extracts of many organs (p. 290), and is probably present in extracts of skin. (ii) The back of a susceptible subject is extensively and severely stroked till a large wheal develops. Under these circumstances the "H"-substance might be expected to be formed in such amounts that some might get into the circulation and produce effects at a distance. It is found that flushing and rise of temperature of the skin of the face occurs like that which follows a subcutaneous injection of 0·06 mgrm. histamine (p. 292).

Effect of Heat and Cold.—(1) If the arm is plunged into a bath of water at 40° to 45° C., marked reddening of the skin takes place. According to Lewis this is due chiefly to dilatation of the minute vessels of the skin partly owing to liberation of "H"-substance and partly to the direct action of the rise of temperature on the capillaries. In addition, reflex dilatation of the larger arteries and veins takes place, which leads to an increased blood-flow through the skin. At *higher* temperatures a typical flare, wheal, and blister are produced due to formation of large amounts of the "H"-substance. If the vessels of an organ are irrigated with saline at 42° C., the dilatation affects first the capillaries and later the arterioles. This change probably occurs during tissue activity when the temperature of the active organ rises (Krogh).

(2) *Cold* produces complex effects: (i) There may be slight pallor of the skin with arteriolar and capillary constriction; this is best seen when skin reddened by warmth is plunged into colder water. *Whitening* of the skin from cold is abnormal and its production is not fully understood. (ii) If the hand is immersed into very cold water (5° to 10° C.) for 5 to 10 minutes, the skin becomes a bright *red* colour which is indistinguishable from that produced at a temperature of 45° C. The arterioles are contracted and the minute vessels are dilated; one would have expected cyanosis to develop (cf. (iii)). At temperatures under 10° C., however, oxyhæmoglobin undergoes very little dissociation, and the oxidative activities of the tissues are also very depressed, so that in spite of the inadequate and very slow blood-flow through the part, the hæmoglobin is not sufficiently reduced to give a dark tint to the blood. (iii) At skin temperatures of 20° to 25° C. *cyanosis* may develop. The vascular changes are similar to those described in (ii); one must presume that at this critical temperature the blood-flow is more reduced than the oxygen utilization by the tissues: consequently the oxyhæmoglobin suffers

extensive reduction and a dusky colour develops. (iv) *Freezing* the skin results in extensive cellular damage and liberation of " H "-substance with the usual triple response.

The phenomena of *Raynaud's disease* may conveniently be considered at this point, though they cannot yet be fully accounted for.

Raynaud's disease is a condition in which the various phenomena of frostbite occur in the projecting parts of the body, either without obvious cause or in response to a degree of cold inadequate to cause such disturbances in normal subjects. The parts affected are usually the fingers and rarely the toes, ears, cheeks, or nose. First the part goes white and cold (syncope), and there is numbness, stiffness, or pain. This may be followed by local asphyxia—the affected area is blue or almost black, cold, slightly swollen, and bedewed with sweat. The condition may culminate in gangrene and casting off of the dead part; or active hyperæmia may occur, and recovery ensue.

Action of Light.—Finsen in his classical experiments exposed the skin to a 40,000 candle-power lamp. The letters NF were painted on the skin in Indian ink, which keeps back all the rays of light. One part of the skin was covered with a plate of rock crystal which lets through the ultra-violet rays, and another with an ordinary glass plate which lets through 90 per cent. of the visible spectrum and keeps back all the ultra-violet rays. After a twenty minutes' exposure the whole arm was uniformly red. This erythema was due to the effect of the heat, and diminished in two hours. After three hours, erythema due to light appeared on the uncovered parts, reached its maximum in twelve hours, and decreased after two days. The redness was associated with capillary dilatation and stasis. The glass plate protected the underlying skin because it kept back the ultra-violet rays, while the rock crystal which allowed these rays to pass through afforded no protection, the erythema beneath it being as marked as elsewhere. Clearly light erythema is due to *ultra-violet rays*. Lewis suggests that ultra-violet rays act by causing a slow liberation of the " H "-substance in the skin. The visible spectrum, however, can also act on the capillaries if it is employed in sufficient concentration and for a long enough time. The erythema in Finsen's experiment disappeared in ten days and was followed by pigmentation and desquamation. The effect on the capillaries was of an enduring nature, because six months later rubbing the arm resulted in the areas which had been exposed in the experiment becoming redder than the other parts of the skin.

TRAUMATIC SHOCK

" Shock " may be defined as a condition in which the sensory and motor parts of the reflex arc are paralysed to a greater or less degree, together with a profound disturbance of the circulation, subnormal temperature, and usually frequent shallow breathing; it may be seen typically following severe injuries. The patient is very still and pays no attention to what is going on around him. The skin and mucous membranes are cold, grey or cyanotic in colour. Large drops of sweat are visible. The pulse is almost imperceptible and very rapid. The arteries are narrowed and the blood pressure is low. The breathing is characterized by long deep sighing respira-

tions alternating with very superficial ones. The patient reacts very slightly and only to very painful stimuli. The limbs are toneless. Spontaneous movements are not made, but in response to urgent orders very brief limited movements may be executed. Complaint may be made of cold, faintness, and deadness of all parts of the body.

Cases of "shock" may be divided into two groups: (1) Early or *primary* shock, which sets in immediately following an injury. It is probably due to afferent impulses causing reflex vaso-dilatation and a profound fall of blood pressure. The diminished blood supply to the brain may result in loss of consciousness. After a time recovery takes place or else the condition may merge into the succeeding one. (2) Delayed or *secondary shock* may set in after a latent period during which nothing obviously abnormal can be noted, or it may follow on primary shock. From the subsequent analysis it will appear that this variety of shock is due chiefly to a *capillary poison*, probably *histamine* or some substance with a similar action which is liberated from the injured tissues.

Factors concerned in Secondary Shock.—(1) The blood vessels in shock are found to be narrowed and the vasomotor centre is not exhausted but still active, for rises of blood pressure can be reflexly produced.

(2) Cannon has shown that crushing the muscles of the hind-limb of an animal may result in a fall of blood pressure down to the level found in shock. This still occurred after all the nerves to the part had been divided, so the effect is not reflex in origin. Shock, however, was prevented if the local blood vessels were clamped to prevent the venous return from the damaged area. Removal of the clamps allowed the characteristic symptoms to appear. These observations strongly suggest that shock is due to some poisonous substance which is liberated from the damaged tissues. There are many reasons for asserting that this substance is histamine or something closely resembling it in its action. (i) Histamine is present in all tissues and is readily liberated as a result of even trivial injuries (p. 296). (ii) *Many of the features of surgical shock are identical with those of histamine poisoning, e.g.* the low venous return, the diminished cardiac output, the low blood pressure, the rapid pulse, the diminished blood volume, the increased viscosity of the blood and the rise in the hæmoglobin percentage, visible distension of the minute vessels in the bowel and the increase in the weight of intestinal loops (p. 290).

Injuries which liberate quite small quantities of this capillary poison may induce shock in the presence of (*α*) an *anæsthetic* which sensitizes the blood vessels to the action of histamine, or (*β*) *other complicating factors* which of themselves tend to lower the blood pressure, *e.g.* (i) exposure to cold; (ii) lack of food and water as was so commonly the case with wounded soldiers in the war; (iii) considerable sweating which for some unknown reason often accompanies severe injuries, causes further loss of fluid, and also tends to lower the body temperature; (iv) hæmorrhage by itself, even if 25 per cent. of the blood volume is lost, does not give rise to a permanent fall of blood pressure, but hæmorrhage combined with injury produces shock. If any of these contributory factors are dealt with, *e.g.* by warmth, blood transfusion, administration of fluid, the shock may be relieved. Pituitrin may be of assistance by restoring capillary tone (p. 292). It is believed too that bacteria may liberate poisons with a histamine-like action, so that the presence of *infection* will greatly aggravate the condition. Abdominal operations are perhaps especially

prone to produce shock because handling of the viscera results in the liberation of the capillary poison in this very important part of the vascular bed.

The low blood pressure and low circulation rate result in the malnutrition of all the tissues. The higher centres suffer most from this anoxæmia so that there is an anxiety, dulness, or apathy; but it is found further that if the blood pressure is kept at about 60 mm. Hg for several hours the medullary centres, and notably the vasomotor centre, fail too, thus tending to perpetuate the state of shock. The *basal metabolism* is diminished and because of decreased heat production (*e.g.* 30 per cent. below normal) the body temperature tends to fall further. The plasma bicarbonate content is lowered in shock; this has been attributed to anoxæmia, which causes incomplete combustion of carbohydrates and possibly of fats in the tissues, with the formation of acid products which pass into the blood.

Henderson has pointed out that excessive pulmonary ventilation washes out the CO_2 of the blood (*acapnia*) and depresses the activity of the respiratory centre. It also prevents relaxation of the heart during diastole so that it cannot receive the venous return; failure of the circulation consequently occurs because the cardiac output is diminished. He has suggested that acapnia may play a part in producing shock, *i.e.* that hyperpnœa is set up by afferent impulses from the injured area or region under operation which reflexly stimulate the respiratory centre. It is doubtful, however, whether hyperpnœa constantly precedes the onset of shock.

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TISSUE FLUID AND LYMPH

The capillaries are a closed system of vessels, and the blood only comes into actual contact with the cells of the tissues in the liver and spleen, where the endothelial lining of the blood spaces is deficient. The cells everywhere else are bathed by *tissue fluid*, which acts as an intermediary, bringing nutritive material and removing the products of metabolic activity.

The lymphatic system includes the tissue spaces, the delicate lymphatic capillaries, and the larger vessels which unite to form the right lymphatic duct and the thoracic duct. The large serous cavities like the peritoneum and pericardium in many respects behave like tissue spaces.

It used to be thought that the tissue spaces opened directly into the lymphatic vessels. This was a very convenient view, because it simplified the question of the disposal of tissue fluid, which was believed to take place by simple drainage into the lymphatic vessels. MacCallum showed that the lymphatics are as closed a system of vessels as is the vascular system. A distinction should therefore be drawn between the fluid in the tissue spaces

(*tissue fluid*) and that in the lymphatic channels, to which the term "lymph" should be restricted. As a rule, however, these distinctions are ignored. It is doubtful, too, whether any stomata are present to connect the serous cavities with the lymphatics. The *composition* of tissue fluid is unknown, but it is assumed to be similar to that of lymph.

Thoracic duct lymph is viscid, opalescent, and faintly alkaline. It contains the same constituents as plasma, but is poorer in proteins (3·5 to 4·3 per cent.) and is richer in salts and water. It varies in composition with the degree of activity of the tissues and may contain much fat. The lymph coming from the liver contains three times as much protein as the lymph from the limbs (6 per cent. against 2 per cent.): that from the intestine is intermediate in its protein content. A certain number of white corpuscles, chiefly lymphocytes, may be present.

The problems that face us are—How is tissue fluid formed, and how is it removed? Probably tissue fluid is derived entirely from the blood; it is removed partly into the lymphatics, and partly back into the blood stream. It is necessary to consider the *physical factors* which may possibly be involved. Certain terms will first be defined.

1. Filtration.—By filtration is meant the passage of water and dissolved substances through a membrane owing to a difference of *hydrostatic* pressure on the two sides of the membrane. This difference of pressure is termed the *filtering force*. The fluid passing through is termed the *filtrate*, and consists of water and any dissolved substances to which the membrane is permeable.

2. Properties of Membranes.—Membranes differ very much in *permeability*, *i.e.* in the size and kind of molecule which is allowed to diffuse through them. Certain membranes only let through water, but are impermeable to dissolved substances, *e.g.* parchment paper, collodion, copper ferrocyanide. The last-named substance is produced when copper sulphate comes into contact with potassium ferrocyanide; the precipitate can be formed in the pores of a porous pot, which is a convenient support for it, by putting copper sulphate inside the pot and potassium ferrocyanide outside. The envelopes of the red blood cells are freely permeable to water, are partially permeable to anions (*e.g.* Cl), but are almost impermeable to kations (*e.g.* Na). Most of the membranes of the body, however, allow water and dissolved crystalloids to diffuse through, but do not permit the passage (to any extent) of the larger colloid molecules; such membranes are often referred to as "*semi-permeable*." In some regions, *e.g.* glomeruli of kidney, the capillary wall allows the passage through it of a fluid identical in composition with the plasma but minus its proteins; most capillaries, however, let through a certain amount of protein, which is greater in the case of the capillaries of the bowel than of the limbs. It must be pointed out that though much is known about the behaviour of dead animal membranes, none of these reproduces the characters of the living endothelial wall of the capillaries. For one thing, the living endothelium is very much thinner (1 μ) than any membrane that has been experimented with (200 μ).

3. Diffusion.—This is the interchange of fluid or of substances in solution between two fluids which are separated by a permeable membrane and which are under the same hydrostatic pressure.

4. Osmotic Pressure.—If a strong sugar solution is placed inside a copper

ferrocyanide pot (which is permeable to water but impermeable to sugar), and the pot is immersed in water, it is found that water passes from the exterior into the interior of the pot and the pressure within it rises to a certain extent. This rise of pressure is a measure of the *osmotic pressure* of the sugar solution ;[1] it is as though the sugar molecules within the pot exerted a *suction action* attracting water to themselves with a certain force.

The osmotic pressure of a solution depends solely on the *number* of molecules in solution and not on their size. If the molecular weight of the dissolved substance expressed in grammes is present in 1 litre of water, it exerts an osmotic pressure of 22·4 atmospheres. For example : the molecular weight of glucose is 180 ; a solution of 180 grm. of glucose in 1 litre of water exerts 22·4 atmospheres pressure ; 0·1 per cent. solution of glucose (=1 grm. in 1 litre, the concentration in blood) exerts $\frac{22{\cdot}4}{180}$ atmosphere

$$=0{\cdot}125 \text{ atmosphere}$$
$$=0{\cdot}125\times760 \text{ mm. Hg}$$
$$=95 \text{ mm. Hg.}$$

For the purpose of osmotic pressure *ions* behave as molecules ; thus a weak solution of NaCl, which is almost completely dissociated into Na and Cl ions, would exert about *twice* the theoretical osmotic pressure as calculated from its molecular concentration.

Osmotic Pressure of Blood.—From the standpoint of osmotic pressure considerations, whole blood may be regarded as consisting of water containing red corpuscles in suspension and inorganic salts and colloids (mainly proteins) in solution. The osmotic pressure of blood is chiefly due to the dissolved inorganic salts and organic crystalloids, but to a slight extent it depends on the blood colloids, chiefly the protein. The calculated osmotic pressure of the plasma is about 6·5 atmospheres, but in the body only a minute fraction of this immense force is available for suction purposes, because under normal conditions the tissues and tissue fluids have about the same salt concentration as plasma, *i.e.* they are isotonic with plasma.

The osmotic pressure of the plasma proteins is of great functional importance because the capillary endothelium is relatively impermeable to protein. It can be determined as follows : An *osmometer* is employed which consists of a small glass bell from the top of which project two vertical pieces of tubing. Over the mouth of the bell is tied the membrane, such as peritoneum soaked in 10 per cent. gelatin which is impermeable to protein ; plasma is placed in the bell and the apparatus is immersed in a solution having the same salt concentration as plasma but free from protein, *e.g.* Ringer-Locke's solution. In the course of a few days it is found that the fluid in the projecting tubes rises to a height of 400 to 500 mm. If one of the tubes is connected to a mercury manometer, a pressure of 30 to 40 mm. Hg is recorded. The proteins have exerted an osmotic pressure of 30 to 40 mm. Hg and have sucked fluid into the bell. As the membrane is permeable to the salts in solution, they also diffuse through, so that the ultimate result is the addition of a certain amount of saline to the plasma.

[1] The osmotic pressure of a solution can be indirectly determined by the depression of the freezing point, which is proportional to the molecular concentrations of solute present.

If the protein concentration in the tissue spaces is lower than in the blood, a force is available which tends to attract fluid into the blood vessels. On the other hand, the capillary blood pressure is a filtering force tending to drive fluid into the tissue spaces, and thus works in the opposite direction to the osmotic pressure of the colloids.

The composition of tissue fluid (as contrasted with lymph) is not known. It must be continuously affected by the products of metabolic activity and by the substances passing into it from the blood.

Any physico-chemical explanation of tissue fluid formation and removal is bound to be incomplete, owing to our ignorance of many essential data.

Tissue Fluid Formation and Removal.—1. Tissue Activity.—In most parts of the body under conditions of rest the balance of the physical forces is opposed to the escape of fluid from the vessels. The protein osmotic pressure is 30 to 40 mm. Hg, while the capillary pressure in the skin in parts above heart level is 4·5 cm. H_2O=3·5 mm. Hg. Only in the most dependent parts, where the hydrostatic pressure of the column of blood is considerable, can the capillary pressure exceed the colloid osmotic pressure. Thus, as we have seen, when the arm is allowed to hang limply it may swell from filtration of fluids outwards into the tissue spaces. Normally, however, the continual slight activity of the muscles and the presence of the venous valves tends to prevent more than a fraction of the hydrostatic pressure from being felt in the capillaries.

During *activity* tissue fluid is formed in considerable amounts. The amount of exudate which takes place from the blood vessels can be determined by comparing the hæmoglobin percentage of the arterial blood entering the part and of the venous blood leaving it and the total blood-flow (Barcroft). The rise of hæmoglobin percentage gives a measure of the loss of fluid. In the case of the *submaxillary gland* the amount of fluid which exudes from the vessels in the resting condition is barely discernible. If the chorda tympani is stimulated or pilocarpine is injected the gland secretes freely, the arterioles are dilated, more lymph escapes from the lymphatic vessels, and there is a great increase in the amount of tissue fluid formed; in ten minutes a volume of tissue fluid which is equal to the volume of the gland may be poured out. If atropine is painted on the gland and the experiment is repeated no secretion of saliva occurs because atropine paralyses the terminals of the secretory fibres in the gland; some arteriolar dilatation takes place (but only for a short period), but little increase in tissue fluid formation is observed. Tissue activity is therefore the controlling factor in tissue fluid formation and not the increased blood-flow (which itself is largely the result of tissue activity (cf. p. 284)).

In resting *muscle*, again, the amount of tissue fluid formed is quite insignificant. In active muscle the exudate amounts to 2 c.cm. per minute per 100 grm. of organ. Thus in one hour a volume of tissue fluid is formed which exceeds the size of the organ itself. This great exudation from the blood persists for some hours after the period of activity is over. It is found, too, that the blood-flow and rate of oxidation in the muscle continue similarly at a high level long after the period of contraction. Eight hours after the end of activity the muscle is 20 per cent. heavier than normal. This increase in weight is accompanied by a lowering of the specific gravity, so that it must be due to the excess of fluid

which is still retained in the tissue spaces. To the naked eye there is obvious œdema of the muscle, which is shorter, of greater girth, and stiffer. This state of the muscle may in part be responsible for the subjective feeling of stiffness which may persist for so long after severe exertion.

In reviewing this experiment we see that an enormous exudate of fluid takes place into the muscle, which is thus provided with the various dissolved substances which it needs for its activity. This exudation remains on a high level for many hours after the activity ceases. This may be associated with oxidative activity in the muscle to dispose of the lactic acid which has been formed during contraction (cf. p. 356).

The *physical* factors are probably these : (i) During activity the large molecules of the resting organ are being broken down into numerous small molecules, and these *metabolites* pass into the tissue spaces. These metabolites are presumed to diffuse very slowly into the blood, and to remain in considerable concentration in the tissue spaces for a long period. They raise the osmotic pressure locally, and so attract fluid from the blood and retain it. The dissolved crystalloids of the blood, which can pass very readily through membranes, diffuse through into the tissue spaces at the same time as the water is being " pulled " there.

(ii) Furthermore, the *capillaries* in the active region are increased in number and widely dilated. Krogh has given evidence that under such conditions the permeability of their wall is increased. This further facilitates the passage of fluid into the tissue spaces. The *blood-flow* through the active organ is very great, and so fresh supplies of fluid are constantly available to make up for the fluid lost to the tissues.

(iii) Owing to the dilated state of the arterioles the blood pressure is transmitted more directly to the capillaries. The capillary pressure probably rises and so filtration from the blood vessels is facilitated.

The fundamental fact, however, is that exudation from the blood vessels is synchronous with, and due to, the functional activity of the organ ; for the metabolites not only raise the osmotic pressure in the tissue spaces, but are responsible for the arteriolar and capillary dilatation as well.

Filtration alone plays a relatively small part under normal resting conditions, because, as stated, the capillary blood pressure is in many places much lower than the colloid osmotic pressure of the blood (cf. p. 303).

Removal of Tissue Fluid.—During the period of activity the tissue fluid which is formed is (i) retained in the tissue spaces, (ii) escapes into the lymphatics, (iii) in the case of *glands* is mainly poured out in the external secretion. On cessation of activity the reparative process may be as follows : Oxidative processes continue in muscle for some time to restore it to its original condition, and exudation of fluid from the blood continues. The metabolites diffuse back again into the blood or are oxidized, and thus the osmotic pressure of the tissue spaces falls. The arterioles and capillaries become narrowed again. Owing to the osmotic pressure of the plasma proteins the excess fluid present in the tissue spaces is absorbed into the blood vessels. As the lymphatics are probably a closed system of channels, no fluid can enter them directly, but must first pass through the endothelial lining. We cannot say definitely how this process is accomplished.

Though tissue fluid is formed by physical processes it is agreed that the

glands or other tissues *select* by means of "vital processes" what they need for their metabolism.

2. Maintenance of Blood Volume.—i. If saline is injected intravenously into a normal animal, a condition of hydræmic plethora results. The excess fluid is accommodated on the venous side of the vascular system, with a consequent rise of venous pressure and a corresponding rise of capillary pressure. The excess of fluid also dilutes the plasma proteins and lowers their osmotic pressure. For these two reasons, *i.e.* the rise of filtering force in the capillaries and the lowering of the antagonistic colloid osmotic pressure, fluid escapes rapidly from the vascular system into the tissue spaces and through the kidneys. The blood volume is thus kept constant. When water is drunk in large amounts, the fluid in excess of that which the kidneys can eliminate is temporarily stored in the tissue spaces (cf. p. 468).

ii. After hæmorrhage, fluid is absorbed into the blood vessels from the tissue spaces by some unknown means (p. 182). During sweating, fluid is mobilized from the tissue spaces to maintain the blood volume (p. 377).

3. Removal of Fluid from the Serous Cavities and Subcutaneous Tissues.—If isotonic saline is introduced into a serous cavity, *e.g.* the pleural cavity, it is absorbed very rapidly. The plasma protein osmotic pressure exceeds in most regions the capillary blood pressure, and so a force is available for absorbing water. The concentration of salts in the pleural fluid rises, and so they diffuse into the blood (as capillary membranes are freely permeable to salts); isotonic saline is thus taken up. The same remarks apply to the absorption of saline from the subcutaneous tissues.

In the case of the pleural cavity, ligature of the thoracic and right lymphatic ducts does not affect the rate of absorption, again proving the fluid is passing chiefly into the blood. If a dye-stuff, *e.g.* indigo blue, dissolved in saline is injected into the pleural cavity, it appears in the urine in five minutes, and in the thoracic duct only after half an hour has elapsed. Absorption into the lymphatics therefore does occur, but is relatively unimportant and slow.

The absorption of blood which has effused into a serous cavity is difficult to explain, because it is identical in composition with the plasma. It is assumed that the proteins of the effusion undergo autolysis and subsequent removal, or are ingested by phagocytic cells. Once the proteins are disposed of, the protein-free plasma can be absorbed because of the osmotic pressure exerted by the blood colloids.

4. It has been thought (Heidenhain) that the capillary endothelium may *secrete* lymph in the same sense as a salivary gland makes saliva—*i.e.* lymph might be elaborated by the vital activity of the living endothelium in spite of the physical forces. No incontrovertible evidence has been produced to support this view. Many observations, it is true, cannot be explained readily on physico-chemical lines, but it is hoped that greater knowledge of the conditions may simplify the matter further.

Œdema.—Œdema is a condition in which there is an abnormal accumulation of fluid in the intercellular spaces. Œdema occurs *physiologically* in muscle during, and for some hours after, activity. The pathological varieties of œdema will now be described, and an attempt made to ascertain the factors responsible for their production.

Abnormal Permeability of the Capillary Wall must first be considered, for this probably plays an important part in the production of œdema. If

a capillary is dilated as a result of the application of urethane, it is found that little or no fluid escapes at the venous end; capillary permeability is so increased that the entire plasma and colloids of the blood filter out, and the corpuscles accumulate in the vessel and clump together, finally filling it completely. The flow in the capillary entirely ceases and but little swelling of the part takes place. If a minor degree of increased permeability occurs, the circulation does not stop, but osmotic balances are disturbed because of the escape of the blood proteins into the tissue spaces. The osmotic pressure of the blood falls and that of the tissues rises, and so fluid remains in excess in the tissue spaces and œdema results. One must imagine that physiological capillary dilatation merely facilitates the interchange of fluid between the blood and the tissues, and that no abnormal escape of protein occurs. If the blood is more dilute than normal, as after hæmorrhage, its holding power for water is diminished and then it is found that even a slight increase in capillary permeability results in œdema.

Lewis has shown (p. 296) that a variety of factors which injure tissues liberate a histamine-like substance in the skin which dilates and increases the permeability of the minute vessels and causes increased exudation of fluid into the tissue spaces, so that wheals may be formed. In susceptible subjects light stroking of the skin may give rise to the flare and wheal (*urticaria factitia*); the injection of histamine into the skin in these cases produces a local response of normal character, so that there is no state of unusual reactivity of the local vessels. It would appear that the precursor of histamine, which is present in the skin cells, is excessively unstable in this disorder, so that very trivial injuries are sufficient to cause the liberation of histamine in sufficient concentration to give the full "triple response." Various poisons taken in the food, or elaborated in the body, or resulting from an anaphylactic reaction, may also give rise to urticaria, possibly by liberating histamine in the skin.

It has been suggested that *calcium salts* diminish capillary permeability. It is claimed that they diminish exudation in inflammation, help in conditions like *chilblains* in which abnormal capillary permeability may be a factor, and prevent the escape of albumin through the glomeruli of the kidneys of subjects suffering from *albuminuria of adolescents*.

1. Venous Obstruction.—i. Œdema often does *not* result if a vein draining a part is obstructed. Œdema occurs, however, if the limb has been previously rendered abnormal by being kept empty of blood or full of stagnant blood for an hour. ii. Owing to the raised venous pressure, the capillary pressure goes up and increased filtration takes place through the capillary endothelium, which is more permeable owing to dilatation. iii. The main factor, however, is the disturbed nutrition of the part; metabolites, therefore, accumulate and raise the osmotic pressure of the tissues, with the result that fluid is retained locally.

2. Cardiac Œdema.—In heart failure from any cause œdema may be a very prominent symptom.

(1) The venous pressure in severe cases of congestive failure is raised from the normal level of 10 to 15 cm. H_2O in the median basilic vein to 30 or 35 cm. H_2O. The capillary pressure must be correspondingly higher, and this tends to filter fluid out into the tissue spaces. This cannot be a very prominent factor, because, as we have seen, a rise of venous pressure is

not necessarily associated with œdema unless malnutrition is present as well.

(2) With a failing circulation there is an inadequate blood supply to the organs. Imperfect metabolism may occur in the tissue cells, and metabolites, instead of being rapidly removed, accumulate in the tissue spaces. The local osmotic pressure rises, and retention of fluid follows.

(3) The raised venous pressure and the metabolites dilate the capillaries, and their permeability is increased; protein escapes into the tissue spaces in excessive amounts and this tends to disturb the water balance between the blood and the tissue cells.

(4) There may be swelling of the tissue cells themselves, as the increased H ion concentration of the colloids enables them to take up more water by imbibition.

(5) The œdema fluid is possibly formed all over the body, and gravitates down to accumulate and become obvious in the dependent parts. It is noticed in the ankles in the evening if the patient is walking about, and passes off during the night. Bolton has suggested that œdema fluid is formed in the neighbourhood of the heart in the visceral peritoneum and gravitates down into the lower limbs, from which the fluid is partly reabsorbed by the lymphatics of the limb.

3. Renal Œdema.—The dropsy varies with the severity and type of case. It may be generalized, or tends to accumulate especially in areas containing loose connective tissue, like the eyelids. It usually varies with position, being most marked in the extremities in the evening, and around the eyelids in the morning. When the œdema is slight, pressure produces a deep impression—"*pitting on pressure*"—but this is slowly effaced by the return of the fluid. In severe cases the face becomes full and rounded, the eyelids are distended, the limbs enlarged and shapeless, and the scrotum and prepuce are greatly swollen. If the skin is incised, 8 to 10 pints of fluid may drain away. Effusion into the serous cavities occurs. The fluid is colourless, sp. gr. 1007 to 1012, and contains a little albumin, inorganic salts, and urea (cf. Œdema fluid, p. 308).

Œdema is a marked feature of *acute glomerulo-nephritis*, in which condition, owing to inflammatory changes in the glomeruli, the blood-flow through the kidney is greatly reduced, with consequent diminution or even arrest of the secretion of urine. Retention of water, salts, and nitrogenous waste products therefore takes place. The blood volume is increased and a rise of blood pressure takes place. The œdema may be regarded in a sense as a compensatory phenomenon, for it enables the excess fluid to be removed from the circulation and to be stored in the tissue spaces. The mechanical factors concerned in the production of the œdema are dilution of the blood, and possibly increased capillary permeability and raised capillary blood pressure.

Extensive œdema is characteristic of a form of chronic renal disease now known as *lipoid nephrosis*, in which glomerular changes are slight and the outstanding pathological feature is degeneration and lipoid infiltration of the tubular epithelium. The disease pursues a chronic course and is distinguished by low urinary output, very marked albuminuria, œdema, and certain negative features such as absence of signs of renal insufficiency, no nitrogenous retention, and no hypertension. This disease has hitherto been

referred to as the " hydræmic " type of nephritis, or chronic parenchymatous nephritis.

The volume of urine may be a few hundred c.cm. daily, the sp. gr. is high (up to 1050), and protein is excreted in large amounts up to 5 to 20 grm. per litre. The œdema fluid has a low protein content (about 0·1 per cent., compared with 0·6 to 1·0 per cent. in acute glomerulo-nephritis) and may contain lipoid. There is no increase in the blood chloride or blood nitrogen, and it is found that if water is ingested it is eliminated slowly but fairly completely; there is little evidence of renal insufficiency, and it is difficult to attribute the œdema to failure of the kidney to excrete salt or water. The principal changes in the blood are: (i) a rise in the cholesterol from 0·15 or 0·2 to 1·0 per cent. or even higher; (ii) a decrease in the plasma protein from 6 to 8 per cent. down to 4 per cent. or even less. Normally the ratio of serum albumin to globulin is 2:1; in nephrosis most of the serum protein may be in the form of globulin.

Epstein regards this disease as a general metabolic disorder with secondary changes in the tubules. Disturbed fat metabolism is indicated by the raised blood cholesterol, and the basal metabolic rate may be reduced to 20 per cent. below normal. According to Epstein, the proteinuria cannot be attributed to increased glomerular permeability, for in that case albumin and globulin should be found in the urine in the same proportions as they exist in the blood; actually, however, the urinary protein consists almost wholly of albumin. He suggests that the serum albumin may be abnormal in some hitherto unrecognized respect, and is therefore excreted by the kidney in the same way as any foreign protein which is injected into the blood stream (*e.g.* egg-albumin, hæmoglobin). The œdema is attributed to the lowered osmotic pressure of the plasma (owing to loss of albumin) which diminishes its power of retaining fluid, altered capillary permeability, and possibly some ill-understood changes in the tissues which result in their retaining excessive quantities of water.

These views have had considerable bearing on treatment. Epstein found that the œdema was frequently relieved by diets rich in protein; he suggests that the ingested protein raises the protein content and osmotic pressure of the plasma, and so causes fluid to flow out of the tissues into the blood. It is well known that ingested proteins are completely disintegrated into amino-acids in the bowel; but there is no doubt that the plasma proteins are ultimately derived from ingested protein, though their site of formation is not known, nor how their appropriate concentration in the plasma is regulated. Epstein attributes considerable importance to the specific dynamic action of the protein, which increases the metabolic rate and may possibly correct the disturbance of oxidative processes in the tissue cells. It has been found that thyroid extract may be of benefit in these cases. MacLean suggests that the protein of the food exerts a diuretic action because it gives rise to urea and other non-threshold bodies which increase the urinary output (p. 471). Thus in one case treated on a high protein diet the plasma protein actually tended to fall, but the blood urea rose from 27 mg. to 60 or 80 mg. per cent., and coincidentally there was a great increase in the urinary flow. MacLean has shown that urea administered by the mouth —*e.g.* 30 grm. daily—is beneficial in relieving the dropsy.

4. Inflammatory Œdema (see p. 209).

5. Œdema of Cachectic States is probably due to the altered permeability of the capillary wall and impaired nutrition of the tissues.

6. Lymphatic Obstruction—*e.g.* from growth, parasitic worms—produces œdema by interference with the removal of tissue fluid.

7. Nutritional Œdema (see p. 452).

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VII

THE RESPIRATION

General considerations—Alveolar air—Laws of gases—Intrathoracic pressure—Gaseous interchanges in the lungs—Douglas bag technique—Respiratory quotient.

General Considerations.—i. Tidal Air is the amount of air breathed in or out of the lungs with every quiet respiration. The average figure is about 400 to 500 c.cm.

ii. Supplemental Air is the additional amount of air which can be expelled after a normal expiration by a maximum expiratory effort. The average figure is 1500 c.cm.

iii. Complemental Air is the amount of air that can be taken in after a quiet inspiration by a maximum inspiratory effort. The average figure is 1500 c.cm.

iv. Vital Capacity is the sum of the preceding figures and is on an average about 3500 c.cm., *i.e.* it is the maximum amount of air that can be inspired after a powerful expiration. It is the deepest breath that we can take, and is about seven times as great as the normal sized breath. The vital capacity varies with the size of the individual and the use to which he has put his respiratory mechanism. It is related to the surface area. It amounts to 2·6 litres per square metre in a male, and 2·07 litres per square metre in a female. Most normal people have a vital capacity within 10 per cent. of these figures. *Athletes* give decidedly higher values, while lower readings are obtained in *old* subjects. It is found (p. 369) that as the depth of the breathing approaches the vital capacity, subjective feelings of discomfort—dyspnœa—develop. The vital capacity is diminished in many diseases, *e.g.* in heart failure (p. 372), various affections of the lung like pneumothorax and tuberculosis, and exophthalmic goitre. Such patients tend to become breathless on exertion more readily than normal subjects.

v. The Residual Air is the air which remains in the lungs after a maximal expiration, and can only be expelled by opening the chest and allowing the lungs to collapse.

vi. Alveolar Air.—As the bronchioles branch and become smaller, their *columnar ciliated* epithelium becomes modified into a *cubical* epithelium. The terminal branches are called *respiratory* bronchioles (Fig. 89), because in places the normal bronchial wall is replaced by patches of thin flattened cells through which gaseous interchanges can take place. Each respiratory bronchiole leads into an expansion, the *vestibule*, from which arise several passages, the *atria*. Each atrium leads into two or three *air sacs* (*infundibula*); the wall of the air sacs is studded with minute evaginations, the *alveoli*. The alveoli are lined by large thin flattened cells, but in places

clumps of cubical granular cells are seen. External to the lining epithelium are yellow elastic fibres and numerous thin-walled blood vessels. This term, alveolar air, does *not* refer to the air which is present in the anatomical alveoli, but is used to describe the air in the *depths of the lung which is more or less in contact with the respiratory epithelium, and can thus carry out gaseous interchanges with the blood.* Alveolar air is a physiological and not an anatomical entity. It consists of the supplemental air and the residual air, and amounts to about 3000 c.cm.

A sample of alveolar air can be collected by the method of Haldane and Priestley. A rapid maximal expiration is made and a sample is obtained of the air which is expelled last from the lungs. The maximal expiration is made (i) after a normal inspiration and (ii) after a normal expiration. The two samples are analysed with the Haldane gas analysis apparatus and the mean of the two results is taken. The average composition of alveolar air is CO_2 4·7 to 6·4 per cent. (average 5·6 per cent.), oxygen about 14 per cent., nitrogen 80 per cent. and saturated with water vapour at body temperature. The average tension of CO_2 is 40 mm. Hg and of oxygen is 100 to 105 mm. Hg.[1]

FIG. 89.—Diagram of Termination of Respiratory Bronchiole.

b=respiratory bronchiole; *v* vestibule; *a*=atrium; *s*=air sac; *c*=alveolus.—After MILLER.

The breathing is normally adjusted to maintain a fairly constant composition of the alveolar air, because the *alveolar air regulates the tension of the gases in the blood.* Enough fresh air has to be introduced into the alveoli to replace the oxygen taken up by the blood, and to get rid of the CO_2 which has come out of the blood. The venous blood which comes to the lungs gives off CO_2 and takes up oxygen until it comes into equilibrium with the air in the alveoli. The tension of the gases in arterial blood is therefore normally about the same as in alveolar air. The arterial gas tensions can consequently be deduced if the alveolar gas tensions are known, so long as the pulmonary epithelium is normal in character.

vii. The *dead space* air is found in the air passages—naso-pharynx, trachea, bronchi. It amounts to 150 c.cm. It does not come into contact with the pulmonary epithelium and carries out no interchanges with the blood.

During inspiration the size of the thoracic cavity is increased. The air in the depths of the lungs follows the outward movement of the chest wall. As the capacity of the lungs is increased, first the dead space air,

[1] The tension of the gases in alveolar air is calculated from the percentage composition thus: the total pressure exerted by all the gases in alveolar air is equal to atmospheric pressure (*e.g.* 760 mm. Hg). Alveolar air is saturated with water vapour at 37° C., which exerts a pressure of 47 mm. Hg; the pressure of the dry gases (CO_2, O_2, N_2) is therefore $760-47=713$ mm. The tension of CO_2 is therefore $\frac{5{\cdot}6}{100}\times 713=40$ mm., and of O_2 is $\frac{14}{100}\times 713=100$ mm.

and later, the fresh air from outside enter the depths of the lungs. One must imagine an interface between the air previously present in the alveoli, and that which has newly entered, across which gaseous interchange occurs. The newly inspired air does not come directly into contact with the pulmonary epithelium. The inspired air during quiet breathing amounts to only one-seventh of the air permanently present in the lungs. The alteration produced in the alveolar air by the fresh air breathed just compensates for the interchanges which are taking place between the alveolar air and the pulmonary blood.

Laws of Gases.—1. At constant temperature, the volume (V) occupied by a gas is inversely proportional to the pressure (P). (PV = constant.)

2. At constant pressure, the volume of a gas is proportional to the absolute temperature (0° C. is 273° on the absolute temperature scale).

3. The partial pressure or tension of a gas, in a mixture of gases having no action on one another, is equal to that which the particular gas would exert did it alone take up the space occupied by the mixture ; in other words, in a mixture of gases at a certain pressure, the pressure is divided between the different gases in proportion to their relative volumes.

4. The amount of gas going into solution in a liquid which has no chemical attraction for the gas depends on its *solubility* and is proportional to the partial pressure of the gas.[1]

Tension of a Gas in a Liquid.—The meaning of this expression is a little difficult to grasp and is best illustrated as follows : If a liquid is exposed for a sufficient length of time to a certain pressure (tension) of a gas, *e.g.* if water is exposed to a pressure of CO_2 of 40 mm. Hg, the molecules of the gas (CO_2) pass into solution in the liquid until equilibrium is reached ; the tension of the gas (CO_2) in solution in the water is then the same as the tension of the gas outside, *i.e.* it is 40 mm. Hg. One must picture the dissolved molecules of the gas as having been "bottled" in the liquid under pressure and these molecules are trying to escape from the liquid with a pressure equal to that with which they were driven in. If the liquid is exposed to a higher CO_2 pressure, *e.g.* 46 mm. Hg, more CO_2 passes into solution ; if to a lower pressure, *e.g.* 35 mm. Hg, CO_2 leaves the solution ; if to the same pressure (40 mm. Hg) no loss or gain of CO_2 takes place. Two gases may be dissolved in a liquid at the *same tension* and yet the *amount* in solution may be very different, depending on the respective solubility

[1] The solubility of the respiratory gases in 100 c.cm. water, plasma, and blood at *38° C.* and *760 mm. Hg* pressure is as follows :

	Water.	Plasma.	Blood.
Oxygen	2·37	2·30	2·30
Nitrogen	1·20	1·20	1·10
CO_2	55·5	54·1	54·1

Note that the solubility is diminished by the presence of salts in plasma and blood, and that CO_2 is far more soluble than either O_2 or N_2.

of the gases. Thus (at 38° C.) 100 c.cm. water which are exposed to a CO_2 pressure of 40 mm. holds about 3 c.cm. CO_2 in solution ; but exposed to the same pressure of O_2 only about 0·12 c.cm. passes into solution (though the tension of the two gases in the water will be exactly the same). The tension of a gas in a fluid may be determined by exposing it to varying gas mixtures of different compositions, and finding with which it is in equilibrium—when no gas is given off or taken up, or by Krogh's method (*infra*).

Intrathoracic Pressure.—The intrapleural space is non-existent in the living animal, as the visceral and parietal layers of the pleura are in contact. The pressure in the pleural cavity is *subatmospheric*, and is −5 mm. Hg during expiration and −10 mm. Hg during inspiration. The pressure in the lungs is about 1 atmosphere, as they are in free communication with the outside air. The full intrapulmonary pressure is not transmitted to the pleural cavity, however, owing to the elastic recoil of the lungs. The more the lungs are stretched, the greater is their tendency to recoil. Consequently, the more the lungs are distended by a deep inspiration, the more subatmospheric (*i.e.* more negative) does the pressure in the pleural cavity become. If the chest wall is opened the pressure on both sides of the lung is atmospheric. The lung consequently collapses in virtue of its elasticity. If the puncture is at once closed, the air in the pleura is absorbed by the blood and the lung re-expands. Similarly, if the lung is collapsed by injecting air into the pleural cavity—*artificial pneumothorax*—it is found that the pleura must be constantly refilled at short intervals if the collapsed condition of the lung is to be maintained.

Gaseous Interchanges in the Lungs.—By means of *Krogh's aerotonometer* the tension of the gases in arterial and venous blood can be determined in experimental animals. A cannula is introduced into the pulmonary artery or into a systemic vessel. The blood to be examined is then allowed to play for many minutes on a small air bubble in the apparatus until equilibrium is established. As the volume of the gas bubble is small and that of the blood which comes in contact with it is very large, the gases in the bubble come into equilibrium with the gases in the blood. By analysing the bubble and determining the gas tensions in it, the blood-gas tensions are known. In the case of man the gas tensions in the mixed venous blood, *i.e.* that in the pulmonary artery, is determined indirectly (p. 260). Arterial blood may be taken directly from a peripheral artery like the radial into a special syringe ; a gas bubble is then introduced into the blood which has been withdrawn and allowed to remain in contact with it until equilibrium is established ; the bubble is then analysed.

When the gas tensions in alveolar air and blood are compared, it is found that the pressure differences are such as would enable gaseous interchange to take place by a simple process of diffusion, *i.e.* because of the difference of gas tension on the two sides of the pulmonary epithelium. The oxygen tension in alveolar air is 105 mm. Hg, and in venous blood it is 40 mm. Hg, *i.e.* there is a difference of pressure of over 60 mm. Hg on the two sides of the membrane ; the corresponding CO_2 tensions are 40 mm. and 46 mm. ; the difference of pressure in this case is quite small, only 6 mm. Hg. As CO_2 passes very readily through the pulmonary epithelium, it can be calculated that this small difference of tension is sufficient to eliminate from the body about 10 litres of CO_2 per minute ; a difference of CO_2 tension across

the lung membrane of 0·12 mm. Hg is sufficient to enable the resting output of CO_2 (200 to 250 c.cm. per minute) to take place.[1]

Oxygen Secretion.—It has been suggested by Haldane that when there is a deficiency of oxygen in the air breathed (*e.g.* at high altitudes) the pulmonary epithelium may after a time actively secrete oxygen from the lungs into the blood, so that the arterial blood may leave with a higher oxygen tension than that found in the valveolar air. This has not been confirmed: Barcroft carried out an experiment in a glass respiration chamber in which the oxygen pressure was gradually lowered. At the end of a week his alveolar oxygen tension was 48 mm. Hg, but the arterial blood was dark in colour and its oxygen tension was *lower* than that in the alveolar air, *i.e.* no evidence of oxygen secretion was obtained.

The Douglas Bag Technique.—By means of this technique, the composition and the quantity of the expired air can be determined under various conditions. A suitably valved mouthpiece is employed, by means of which atmospheric air is breathed in, and the expired air is collected for five minutes in a large canvas Douglas bag of 100 litres capacity or more, and is then analysed in a Haldane's gas analysis apparatus. The CO_2 is absorbed by means of potash, and the oxygen by alkaline pyrogallic acid. The volume of the expired air is measured by passing it through a spirometer. The oxygen consumption and CO_2 output can thus be determined. *e.g.*

Pulmonary ventilation per minute, 5 litres.
Inspired air, O_2 20·96, CO_2 0·03 per 100 c.cm.
Expired air, O_2 16·0, CO_2 4·0 per 100 c.cm.

$\therefore$ O_2 consumed is 250 c.cm.; CO_2 output is 200 c.cm. per minute.

The *respiratory quotient* (R.Q.) is the ratio of CO_2 evolved / O_2 absorbed. In the above example it is $\frac{200}{250}=0{\cdot}8$.

The R.Q. can thus be determined under varying conditions of diet, health, and disease.

1. On a mixed diet it is 0·8 to 0·85.
2. On a purely carbohydrate diet it is 1.

$$C_6H_{12}O_6+6O_2=6CO_2+6H_2O$$

i.e. the amount of CO_2 evolved is equal to the oxygen retained.

3. On a purely fat diet it is 0·7.

$$C_3H_5(C_{18}H_{33}O_2)_3+80O_2=57CO_2+52H_2O.$$

As fat contains very little oxygen, it must be provided in sufficient amount to oxidize both the hydrogen and the carbon of the fat molecule.

[1] The velocity of exchange of a gas between the lungs and the blood depends on: (i) pressure difference. (ii) solubility of the gas in blood. (iii) the properties of the membrane. Velocity of exchange=

$$\text{Pressure gradient} \times \text{solubility of gas} \times \frac{0{\cdot}139}{\sqrt{\text{density of gas}}} \times \frac{\text{area of lung}}{\text{thickness of lung}}.$$

The pressure gradient in the case of CO_2 is one-tenth that of O_2, the density of CO_2 is 44 compared with 32 for O_2, but CO_2 is about twenty-five times as soluble as O_2. CO_2, therefore, diffuses out more quickly than O_2 enters the blood in spite of the disparity in the pressure gradients for the two gases.

4. On a protein diet it is about 0·8.

5. Conversion of fat into carbohydrate and *vice versa* (p. 430).

6. In diabetes it falls to 0·7, and rises to normal if sufficient insulin is administered (pp. 419, 421).

7. Respiratory quotient of excess metabolism of exercise (p. 359).

If the R.Q. and oxygen consumption are known, the *energy* output of the body can be indirectly determined with the aid of tables (p. 318).

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REGULATION OF THE BREATHING

Respiratory centres—Breathing and metabolism—Measurement of metabolic rate—Factors influencing it—Action of CO_2—H ion concentration—Specific action of CO_2—CO_2 excess and lack—Effect of oxygen lack—Compensation—External conditions—Apnœa—Cheyne-Stokes breathing—Action of vagi—State of centre—Other factors.

The Respiratory Centre.—The older workers showed that if the brain stem is trans-sected from above downwards, all breathing movements cease when the section divides the medulla oblongata at the level of the apex of the calamus scriptorius. The respiratory centre was consequently located in this region, close to the central terminations of the vagus nerve. The centre is bilateral, longitudinal section of the medulla in the middle line being without effect. From the centre, fibres descend in the lateral columns of the spinal cord to control the nuclei supplying the various muscles of respiration. There is some evidence to show that each half of the centre can control the spinal nuclei of both sides.

If the spinal cord is divided high in the cervical region above the origin of the phrenic nerves, and no artificial respiration is provided, irregular and inco-ordinated movements of the respiratory muscles occur which are probably asphyxial in origin and analogous to the convulsive movements which take place in the limbs.

Lumsden has recently reinvestigated the matter and has shown that the respiratory centre is a more complex structure than has hitherto been suspected. If the trans-section is made in the *midbrain*, the breathing continues in normal fashion. As soon as the hinder limits of the inferior colliculi are passed and the section involves the *upper pons*, a new type of breathing appears. A slow deep inspiration is taken, and the inspiratory position of the chest is held for two or even three minutes. During the latter part of this inspiration the muscles slowly relax and finally give way suddenly and the air is expelled from the chest. Two or three relatively quick respirations of abnormal type occur, and following these another prolonged inspiration appears. The cycle may repeat itself with great regularity for some hours, but the duration of the inspirations gradually lessens. These prolonged inspirations Lumsden refers to as *apneuses* (*ἀπνευστία*, a holding of the breath), and this type of breathing can be called apneustic breathing (Fig. 90).

When the section is in the region of the *striæ acusticæ*, rhythmic respiration continues, but now consists of a series of *gasps*. Inspiration and expiration begin and end suddenly, and are followed by a pause. Division of the medulla oblongata at the level of the apex of the *calamus scriptorius* causes the cessation of all respiratory movements and death.

To explain these phenomena, Lumsden postulates the presence of a series of centres in the lower brain stem, each of which is released if the centre above it is destroyed. In the upper medulla, below the striæ acusticæ, is a *gasping centre* which, when working alone, causes gasping respirations. It is probably of little importance, and represents an evolutionary relic. Just above the

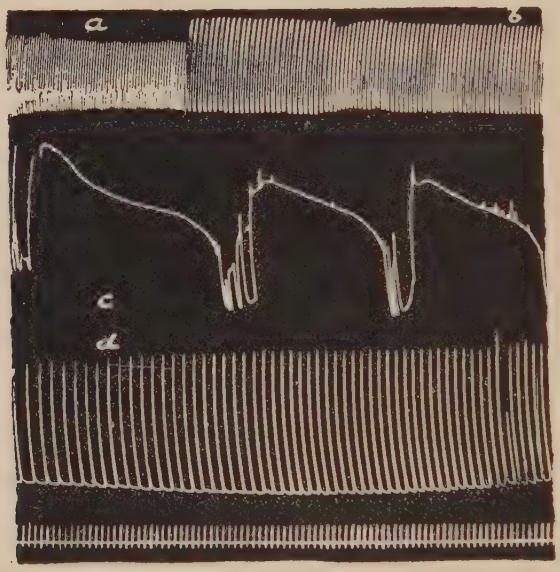

Fig. 90.—Record of Respiratory Movements.

a. Normal; *b*. Slow deep breathing following double vagotomy; *c*. Apneustic breathing interspersed with gasps; *d*. Gasping breathing (see text). (Lumsden, *Journ. Physiol.*)

level of the striæ acusticæ is the *apneustic centre*, which is responsible for the prolonged inspirations. In the region of the upper pons is a centre which normally checks the activity of the apneustic centre and so produces normal respiration. The nerve cells having this effect are called the *pneumotaxic* centre.

The sequence of events in quiet respiration may be as follows: The gasping centre can be ignored, as it plays no part at all. The apneustic centre initiates the inspiratory movement, which is not allowed to continue for long, but is rapidly cut short by the higher pneumotaxic centre. Expiration is thus passive in character and is brought about by simple inhibition of inspiratory activity. The midbrain has no appreciable influence on respiration.

Division of the *vagi* has no effect on these different types of breathing

except to slow them in the usual way (p. 328). Stimulation of the central end of the vagus has a marked checking effect when apneustic breathing is in force.

When the animal is dying from asphyxia, overdose of anæsthetics, or interference with the blood supply to the medulla, the different parts of the respiratory centre cease functioning from above downwards. From being regular, the breathing becomes apneustic; then prolonged inspirations interspersed with gasps appear, and finally life is maintained for a short time by gasps alone. Conversely, if the animal is revived by means of artificial respiration, the breathing returns in the reverse order.

An *expiratory* centre is described by Lumsden just below the region of the striæ acusticæ, which is similarly controlled by the *pneumotaxic* centre. In quiet breathing it plays little part, except perhaps slightly to increase the tone of the expiratory muscles during expiration. During deep breathing, expiration becomes active. The expiratory centre comes into play and the normal expiratory muscles contract. In more severe cases, *e.g.* in *asphyxia*, the contraction of the expiratory muscles becomes a tetanic spasm, and the accessory expiratory muscles contract too. The abdominal contents are compressed and the diaphragm is pushed up into the thorax. The tetanic spasm passes into a series of clonic movements, and generalized convulsions and vomiting may ensue.

Kirkwood and Myers have reported cases in infants in which apneustic breathing was noted following birth injuries. Post mortem, Lumsden was able to demonstrate hæmorrhages in the pons.

Regulation of the Breathing.—We shall better understand the regulation of the breathing, if we pause to consider the purpose of respiration. The self-evident reason for breathing is to obtain supplies of oxygen and get rid of CO_2 formed in the body. Our oxygen requirements and the amount of CO_2 liberated are proportional to the degree of activity of the body. The first law of breathing is therefore (all other things being equal), that the *pulmonary ventilation is proportional to the metabolic rate.*

We already know (p. 224) that the respiratory centre is extremely sensitive to the slightest change in the H ion concentration of the blood and responds in such manner as will keep the reaction at its normal level. The second great principle to remember is that the *pulmonary ventilation will vary with the reaction of the blood.* Under exceptional conditions the breathing is varied to maintain the normal *temperature* of the body.

Breathing and Metabolism.—When an individual is at complete rest 12 to 18 hours after a meal, considerable metabolic activity is still continuing, although no physical work is done and the digestion and absorption of the last meal have been completed. This is termed the *basal metabolism*, which is found to be related chiefly to *the surface area of the individual.* As a result of this basal metabolism, oxygen is consumed, CO_2 is given off, and much energy is liberated. Some of this energy is utilized to maintain the activities of the vital organs,—*e.g.* heart, brain, glands,—and the rest is converted into heat to maintain body temperature and prevent it from falling below the normal level. The energy produced can be measured directly in a calorimeter or deduced indirectly.

For the indirect method all that is necessary is to collect the expired air in a Douglas bag for a few minutes. The expired air is analysed by means

of a Haldane gas analysis apparatus and its volume measured with a spirometer. The composition of the inspired air is known—it is ordinary atmospheric air. In this way the oxygen consumption per minute and the respiratory quotient (ratio of CO_2 evolved over oxygen retained in the body) can be worked out.[1] All the energy produced in the body can, for the sake of simplicity, be assumed to be derived from varying proportions of carbohydrate and fat. The metabolism of protein we shall see, apart from the nitrogenous fraction which is excreted, is essentially that of its carbohydrate and fatty residues (p. 435). From the following table (from Douglas and Priestley) the caloric equivalent of each litre of oxygen consumed may be calculated:

R.Q.	Calories evolved per Litre of Oxygen consumed.
0·71	4·795
0·75	4·829
0·80	4·875
0·85	4·921
0·9	4·967
0·95	5·012
1·0	5·058

It will be noticed that whenever 1 litre of O_2 is consumed in the body 4·8 to 5·0 calories are evolved, the exact amount varying with the foodstuff that the body is using; if fat alone is used (R.Q. = 0·7) the caloric output per litre of O_2 is 4·8, if carbohydrate alone is used (R.Q. = 1·0) the caloric output is about 5·0.

It is found, as has already been pointed out, that the basal metabolism is closely related to the surface area and is less directly related to height or weight. The surface area can be calculated from the following formula if the height and weight are known (Du Bois). $A = W^{0·425} \times H^{0·725} \times 71·84$, where A = surface area in sq. cm., W = weight in kg., and H = height in cm. In the male 40 calories, and in the female adult about 37 calories are given off every hour per square metre of body surface (the surface area of an average adult is about 1·8 sq. metres); or, expressed in terms of body weight, the basal metabolism amounts to about 1 calorie per kg. per hour.

As can readily be seen from the table quoted above, each litre of oxygen when used liberates (R.Q.: 0·8) about 4·87 calories on the average,

i.e. the *oxygen intake per calorie* is $\frac{1000}{4·87}$

$= 210$ c.cm. approximately.

Man: 70 kg. weight and 160 c.cm. height: surface area = 1·73 sq. metres.

$\therefore$ Basal metabolism per hour (40 calories per sq. metre per hour)

$= 40 \times 1·73 = 69·2$ calories; $\frac{69·2}{60} = 1·15$ calories per minute.

As each calorie involves an oxygen intake of 210 c.cm.,

$\therefore$ Oxygen consumption $= 1·15 \times 210 = 242$ c.cm. per minute.

[1] Cf. p. 314.

From every 100 c.cm. of inspired air about 5 c.cm. of oxygen are obtained.

So *pulmonary ventilation* at rest is $\frac{242}{5} \times 100$=about 5 litres per minute.

In the case of a woman it can similarly be shown that the basal pulmonary ventilation averages about 3·5 litres per minute.

The pulmonary ventilation in the adult under basal conditions varies from 2·5 to 5·5 litres per minute.

It is clear from the above considerations that any factor which modifies the metabolic rate will produce corresponding alterations in the pulmonary ventilation.

Factors Influencing Metabolic Rate.—1. Under basal conditions the metabolic rate depends on the surface area (and therefore indirectly on the height and weight) and the sex of the individual (p. 318).

2. *Age.*—The basal metabolism is considerably greater per sq. metre of surface in *children* than in adults, *e.g.* age 6, 57·5 C; age 12, 50·4 C; age 13·7, 49·4 C; age 16·5, 43·0 C (Du Bois). There is a further gradual fall in the metabolism during adult life as age advances, *e.g.* (for males), age 20 to 40, 40 C; 40 to 50, 38·5 C; 50 to 60, 37·5 C; 60 to 70, 36·5 C; 70 to 80, 35·5 C (a corresponding diminution also occurs in females) (Fig. 91).

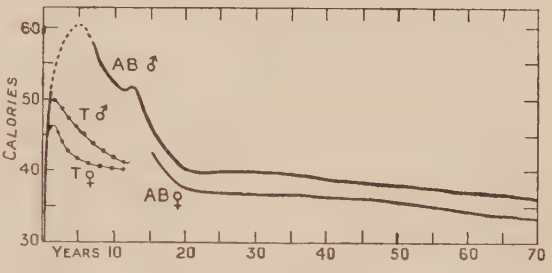

Fig. 91.

Abscissa=Age in years; Ordinate=Calories per sq. metre per hour; AB ♂ and ♀ = Metabolic rate at different ages in males and females respectively, according to Aub and Du Bois; T ♂ and ♀ Metabolism in male and female children at different ages, according to Talbot.

3. *Starvation* or prolonged *undernutrition* damp down the metabolic rate. For example, in a man who had fasted thirty-one days, the daily basal metabolism diminished from 958 to 737 calories per sq. metre of surface area—a fall of over 20 per cent. The same may be said of the diabetic who has been treated by the modern method of generally restricted diet. In such patients the body weight is maintained on considerably less than the theoretical basal calorie requirements. Undernutrition therefore diminishes the pulmonary ventilation.

4. It has been shown that for every rise of 1° F. in the internal *temperature* of the body, the basal metabolism increases by 7·2 per cent. The chemical reactions of the body, like those occurring in a test-tube, are speeded up by a rise of temperature. A patient suffering from pneumonia with a temperature of 105° F. (about 7° F. above the normal) would have an increase of 50 per cent. in his metabolism and in his pulmonary ventilation because of the fever alone.

5. *External Temperature.*—Exposure to *cold* increases the metabolism in order to raise heat production to maintain the normal body temperature (p. 132). Exposure to external heat of brief duration has little effect on

metabolism, as compensation is effected mainly by increasing heat loss ; if the exposure is prolonged a gradual fall in the metabolic rate takes place (p. 375).

6. The active principle of the thyroid gland—thyroxine—appears to act as a general catalyst, facilitating and speeding up the metabolic activities of the tissues (p. 155).

Thus in exophthalmic goitre, in which there is increased secretion of the active principle of the gland, the basal metabolism and consequently the pulmonary ventilation may increase up to double the normal in a severe case. In myxœdema, in which there is lessened secretion of thyroxine, metabolic activity is depressed to 60 or 70 per cent. of the normal, and the pulmonary ventilation is diminished accordingly.

7. Adrenaline increases the metabolic rate, but to a less extent than thyroxine. The injection of 1 mg. adrenaline in man increases heat production by about 20 per cent. for a short time (p. 129).

8. In certain other conditions there is an increased metabolic rate for no very clear reason. This is seen in both varieties of *leukæmia*, in which the increase is of the same order as that found in Graves's disease. A less marked increase is found in *pernicious anæmia* and in *heart disease* when decompensation, *i.e.* failure to maintain an adequate circulation, is present. Besides the other factors tending to produce dyspnœa in heart failure, there is this additional load on the pulmonary bellows because of the increased metabolic rate.

9. The taking of *food* stimulates the body metabolism. This effect is not equally marked with all classes of food-stuffs, being least with carbohydrate and fat, and most definite with protein. If 500 grm. of meat are consumed, the metabolism and the pulmonary ventilation rise two hours later by about 20 per cent., and this is maintained for about four hours. In the case of carbohydrate and fat in amounts of equal calorie value, the metabolism only increases 5 or 6 per cent. This peculiar property of proteins is often termed their " specific dynamic action." This drug-like stimulation of the metabolism is attributed to the fatty acid residues which are left after the NH_2 groupings have been removed from the amino-acids. If an ordinary mixed diet is taken the metabolism is increased by about 150 calories daily.

10. Lastly, and most important, there is an increase in the metabolism with muscular *work*. During very violent exercise the oxygen consumption per minute may rise from 250 c.cm. to 4 or even 6 litres, *i.e.* the metabolism may increase 16 to 24 times. The pulmonary ventilation goes up in direct proportion, and may reach 50 to 100 litres per minute.

The Nature of the Respiratory Stimulus.—We must now consider the way in which metabolic activity produces its effects on the respiratory centre. Various possibilities suggest themselves, *e.g.* the increase in the carbon dioxide of the blood, the increase in the H ion concentration which may conceivably accompany it, or the lack of oxygen. Probably all these factors play some part.

CO_2 and Breathing.—Ordinary room air contains negligible amounts of CO_2 (0·03 per cent.). If air containing excess of CO_2 is breathed, the pulmonary ventilation increases in a very striking manner. In fact, a quantitative relationship is found to exist between the CO_2 in the inspired air and the pulmonary ventilation, so that the extent of the latter can be accurately

predicted (Scott). The alveolar air constantly receives CO_2 from the venous blood, and this gas is normally washed out from the lungs by the fresh air breathed. It follows that if the inspired air contains much CO_2, it cannot eliminate CO_2 so well from the alveoli if the breathing remains of the same extent. The alveolar CO_2 therefore rises slightly. As the arterial blood leaves the lungs in equilibrium with alveolar air, the arterial CO_2 tension also rises. The respiratory centre is consequently stimulated. The ventilation is increased, more air is breathed, and that compensates for its being contaminated with CO_2. The alveolar CO_2 is thus reduced practically to its normal level. As the air breathed still contains excess of CO_2, the alveolar CO_2 can never fall quite to normal. For should the breathing lower the alveolar CO_2 to normal, the excessive stimulus to the respiratory centre ceases. The moment breathing becomes of normal extent, the alveolar CO_2 rises once more. What happens is that so long as CO_2 is present in excess in the inspired air, the pulmonary ventilation is increased and the alveolar CO_2 is thus kept practically normal. As soon as fresh air is breathed again, normal pulmonary ventilation and alveolar CO_2 obtain once more.

Percentage CO_2 in Inspired Air.	Average Depth of Respiration.	Average Frequency per Minute.	Ventilation of Alveoli with Inspired Air.	Percentage CO_2 in Alveolar Air.
0·04	673 c.cm.	14	100 taken as normal.	5·6
0·79	739 c.cm.	14	116	5·5
2·02	864 c.cm.	15	153	5·6
3·07	1216 c.cm.	15	226	5·5
5·14	1771 c.cm.	19	498	5·2
6·02	2104 c.cm.	27	857	6·6

These facts are well shown in this table from Haldane and Priestley. It will be noticed that the breathing increases first in *depth* and later in frequency, the increase in depth contributing considerably more to the increased ventilation. The limits of the compensatory mechanism are also shown. If the CO_2 in the inspired air exceeds that in the alveoli, *e.g.* 6·02 per cent., no possible degree of ventilation will keep the alveolar CO_2 below that figure. As CO_2 is also arriving in the venous blood, the alveolar CO_2 may rise higher still, *e.g.* to 6·6 per cent.

H Ion Concentration and Breathing.—The question arises whether CO_2 has any specific action on the respiratory centre, or whether it acts solely in virtue of its affecting the H ion concentration of the blood. It can be shown conclusively, however, that changes in blood reaction will influence the activity of the centre (cf. p. 224).

During gastric secretion HCl is eliminated from the blood, with a consequent tendency to alkalæmia. The same effect is produced by the ingestion of $NaHCO_3$ by the mouth, which is absorbed as such into the blood stream. Again, a vegetable diet contains a relative excess of basic radicles, and so tends to increase the alkalinity of the blood. We would therefore expect the respiratory centre to be depressed, the pulmonary ventilation to diminish, and the alveolar CO_2 to rise. This rise of alveolar CO_2 has actually been

demonstrated in all the conditions enumerated. It obviously tends to raise the arterial CO_2 tension, and consequently the H_2CO_3 content and the concentration of H ions in blood, and thus compensates for the alkalæmic tendency.

Conversely, a tendency to acidæmia can be induced in various ways and shown to lower the alveolar CO_2 tension, presumably because the respiratory centre was stimulated and the pulmonary ventilation increased. This occurs during pancreatic secretion, when Na_2CO_3 is excreted, leaving a relative excess of H ions in the blood. A meat diet gives rise to excess of acid radicles, especially H_3PO_4 and H_2SO_4 derived from the oxidation of the P and S of the protein molecule, and the alveolar CO_2 is found to fall. If ammonium chloride is ingested, the NH_3 portion is split off, combined with carbonic acid and converted into urea. The HCl which was previously combined with NH_3 is liberated, tends to produce acidæmia with resulting hyperpnœa and fall of alveolar CO_2 tension.

This is the evidence on which we based the statement that one of the great laws of the breathing is, that it is adjusted to maintain the normal reaction of the blood.

Specific Action of CO_2.—Some animal experiments have been carried out which suggest that CO_2 acts as a respiratory stimulus not solely because it dissolves in blood to form H_2CO_3 and thus gives rise to H ions, but that it also has some *specific* action on the centre apart from its properties as an acid. The reaction of blood depends on the ratio $\frac{H_2CO_3}{NaHCO_3}$. It is possible to lower the H ion concentration either by increasing the $NaHCO_3$ (and leaving the H_2CO_3 content untouched) or by lowering the H_2CO_3 alone.

1. By means of excessive artificial respiration, CO_2 is washed out from the blood and its alkalinity increased. When a *p*H of 7·8 (normal *p*H 7·4) is reached, natural breathing can no longer take place. Apparently no adequate stimulus to the respiratory centre is available. If the *same* degree of alkalinity is induced by injection of $NaHCO_3$ the breathing continues. The blood reaction is the same in the two experiments, yet the effect on the respiratory centre is different. In the second case the H_2CO_3 content of the blood was unaffected, and so the breathing persisted in spite of the low H ion concentration.

2. If the vessels of the medulla oblongata are perfused with blood in which the H ion concentration is maintained by H_2CO_3, the response of the centre is greater than when the same H ion concentration is maintained by some other acid like HCl.

It must be pointed out in respect of this last experiment that under normal conditions the cH of blood is always maintained by H_2CO_3 and not by foreign acids, which, as stated (p. 221), are at once buffered by the $NaHCO_3$ of the plasma, liberating H_2CO_3. The first series of experiments may be explained on these lines. It is probably not the reaction of the *blood* which affects the respiratory centre, but the reaction within the *nerve cells* composing it. Jacobs studied the changes in the reaction of cells when placed in media in which the same H ion concentration was maintained by a series of different acids. The greatest rise of cH inside the cells occurred when H_2CO_3 was present in the surrounding fluid. Apparently the cell membrane is relatively impermeable to H ions as such, but readily permits the passage of undissociated H_2CO_3 through it. We have noticed (p. 313) how easily

H_2CO_3 diffuses through the pulmonary epithelium. Once inside the cell it dissociates and raises the cH of the cytoplasm, and this acts as the effective stimulus to the respiratory centre. It is clear, then, that if two fluids have the same cH, but one has a higher H_2CO_3 content, more of this acid will penetrate the substance of the respiratory centre. The response obtained will be greater than in the case where the H_2CO_3 content of the blood is lower (although the reaction of the two fluids is the same).

Effects of Excess of CO_2 in Man.—When air containing 3 per cent of CO_2 is inspired, the increased depth of breathing is noticeable subjectively at rest. On exertion, unusual hyperpnœa develops and the power to do hard work is impaired.

With 4 per cent. CO_2 in the inspired air, the frequency of the breathing increases, and the pulse becomes rapid and full. The alveolar CO_2 shows, as a rule, a rise of about 0·5 per cent. With further rise of CO_2 percentage, compensation becomes more difficult, and with 6 per cent. CO_2 headache and mental confusion develop. With higher percentages of CO_2 toxic effects appear: the heart slows, consciousness is lost, the breathing becomes feeble and finally ceases.

Symptoms of CO_2 excess are uncommon in disease in man, unless there is actually some obstruction in the respiratory passages. Poisoning with CO_2 can never happen inadvertently, because of the immediate choking sensation aroused. Death in mines and wells is usually due to oxygen lack or to the effects of carbon monoxide.

Effects of CO_2 Lack.—The alveolar CO_2 tension under conditions of rest is normally fairly constantly at a uniform level, except during the adaptations to the secretion of digestive juices or other adventitious events.[1] If the level of the alveolar CO_2 is arbitrarily kept lowered by excessive artificial respiration or by voluntary forced breathing below its accustomed level, the respiratory centre may cease to send out its normal rhythmic impulses, and *apnœa* or cessation of breathing occurs (see p. 325).

Effect of Oxygen Lack on Breathing.—It would be expected that considering that one of the purposes of breathing is to supply the oxygen needs of the body, that oxygen lack would act as a potent stimulus to the centre. The question is complicated, however, by the effect of oxygen lack on other parts of the body, and the effects differ very strikingly according as to how acutely the oxygen deprivation is produced.

1. If an inert gas like nitrogen is breathed, the CO_2 is eliminated quite normally from the alveoli, but the oxygen present there is washed out as well. Not only does the venous blood reaching the lungs soon cease to gain any oxygen, but when the oxygen content of the alveoli falls sufficiently, the venous blood gives up its oxygen and the arterial blood passes away completely reduced. No hyperpnœa occurs as a rule, but within forty-five seconds loss of consciousness develops suddenly, and practically without any warning, from oxygen lack to the brain. There are no reserve stores of oxygen in the tissues (unlike CO_2); the only oxygen present there being the minute amounts which are present in solution.

2. If the oxygen lack is less severe, the effects produced depend on how rapidly it is induced.

[1] Cf. pp. 224 *et seq.*, 321, 324, 325, 326, 330, for conditions under which alveolar CO_2 may be altered.

If the subject breathes in and out of a large bag through a soda lime chamber, the CO_2 evolved is removed by the soda lime and does not therefore accumulate in the bag. The oxygen content gradually diminishes. The breathing is unaffected till the oxygen in the bag is reduced by about one third, *i.e.* from 21 to 14 per cent. In some sensitive subjects considerable increase in the breathing may now occur; but as a rule the increase is too slight to be appreciable subjectively, though it can be shown to be taking place. It contrasts very strikingly with the intense hyperpnœa which results from even a small rise of CO_2 in the inspired air. The respiratory centre responds to oxygen lack, but to nothing like the extent to which it reacts to CO_2 excess. The effect of the increased breathing is again to raise slightly the oxygen content of the alveoli, and to wash out excessive amounts of CO_2. As the blood becomes better oxygenated and its CO_2 content steadily falls, the breathing dies down again and never gets a chance to be maintained at a permanently high level. There is a tendency, too, for the breathing to wax and wane, *i.e.* be "periodic" in character. The effects may be summarized thus:

Oxygen lack—stimulates respiratory centre—increases pulmonary ventilation—lowers alveolar CO_2—lowers arterial CO_2—alkalæmia—depresses respiratory centre.

Effective compensation is thus not established, and the stimulus of oxygen lack to the respiratory centre constantly tends to be counteracted. Cyanosis develops when the oxygen content of the inspired air falls to 10 per cent., and this is accompanied by marked mental incapacity. Consciousness is lost a little later, from oxygen deprivation of the higher centres, without any air struggle. In animals, death would be found to occur quite peacefully.

3. The results are different when oxygen lack is of very gradual onset, and ample time is available for all the compensatory activities of the body to be brought into play. This is well seen on ascending gradually to high altitudes.

No symptoms occur till a height of about 11,500 feet is reached which corresponds to a barometric pressure of about 500 mm., *i.e.* two-thirds of the normal level. If the ascent is rapid, the earlier phenomena described in paragraph 2 (*supra*) may occur—slight breathlessness, cyanosis, and periodic breathing, which latter is not present continuously but is readily brought about by holding the breath or occurs at night during sleep. The periods are short, consisting of three to six breaths separated by a pause, and are due to the jerky working of the centre when it is controlled by oxygen lack.

It is clear that the main stumbling-block in the way of an effective respiratory response to oxygen lack is the alkalæmia induced by the excessive washing out of CO_2 from the blood, which tends to depress the activity of the respiratory centre. It is found, however, that after staying for some time in rarefied atmospheres the breathing is maintained at a much higher level than normal, in spite of the lowered alveolar (and arterial) CO_2 tension. Thus at Pike's Peak in Colorado, when acclimatization had taken place, the pulmonary ventilation had increased from 10·4 to 14·9 litres per minute, and the alveolar CO_2 tension was 27 mm. Hg instead of the normal 40 mm. Hg. The observations of Somervell during the recent (1924) Everest Expedi-

tion are even more striking.[1] At Phasi Dzong (altitude 14,300 feet) the average alveolar CO_2 tension was 28 mm. Hg; at 16,500 feet up, it was 19 mm. Hg; at 23,000 feet (barometer 330 mm.) it was 8 mm. Hg! The breathing at these great heights was very rapid, about 55 to the minute, and very deep. At 28,000 feet Somervell found that for every single step forward and upward seven to ten complete respirations were required. Figures for the pulmonary ventilation are not given, but it must have been very great. Breathing quickly and deeply was very easy at high altitudes owing to the low density of the air.

To enable such enormous ventilation to go on in the face of the low arterial CO_2 tension, it is obvious that the alkalæmia must be compensated for in some way. This is done by the kidney, which excretes a less acid urine and less ammonium. The urine may even become alkaline. In this way the kidney eliminates the excess of base, keeps the blood reaction fairly constant, and thus permits oxygen lack to continue to stimulate the respiratory centre.[2]

i.e. O_2 lack—increases pulmonary ventilation—alkalæmia—compensated by kidney (cf. Fig. 65).

It was originally thought that oxygen lack prevented the complete combustion of carbohydrates, and consequently lactic acid accumulated which produced an acidæmia and thus stimulated the breathing. There is no evidence in support of this statement as far as high altitudes are concerned, and the response of the kidney definitely argues in favour of a compensatory activity secondary to an alkalæmia induced by hyperventilation. We may say that oxygen lack definitely stimulates the respiratory centre, or, as some authors prefer it, that it *sensitizes* the centre to the stimulus of CO_2.

As a rule, the increase in breathing due to oxygen lack is chiefly in rate and not in depth, thus contrasting with the effects of CO_2 excess. With marked oxygen lack the respiratory centre fails, as shown by great shallowness and rapidity of the breathing.

External Conditions.—When the body is exposed to warm and very moist external surroundings, regulation of body temperature becomes very difficult as heat loss by evaporation and radiation from the skin are greatly interfered with. The pulmonary ventilation under these conditions is greatly increased in order to eliminate more water vapour in the expired air and thus get rid of heat from the body. The alveolar and arterial CO_2 tension fall, and the alkalæmia resulting is compensated for by the excretion of an alkaline urine (cf. pp. 224 *et seq.*, 378).

Apnœa.—If a person who is at bodily rest breathes very deeply and quickly for two or three minutes and then allows his respiratory centre to act independently of voluntary control, it is found that a period of *apnœa* (cessation of rhythmic breathing) ensues which lasts for about two minutes. In many people a phase of *periodic* breathing then follows which gradually dies away (Fig. 93).

[1] The alveolar air figures quoted probably cannot be relied on, because the samples were stored in rubber bags through which CO_2 can diffuse out fairly readily.

[2] For other compensatory reactions to oxygen lack, see p. 338.

Fig. 92 shows the results of analysis of the alveolar air during the course of the experiment. At the end of the period of hyperventilation, the oxygen content of the alveoli is very high—the tension being 140 mm. Hg (instead of the normal 100 mm. Hg). As CO_2 is washed out from the lungs more rapidly than it is passing out from the venous blood, the alveolar CO_2 tension is low—about 15 mm. Hg (normal 40 mm. Hg). If we regard the arterial CO_2 tension as being in equilibrium with the alveolar air, it is obvious that the CO_2 tension in the blood is far below the minimal level necessary for activity of the respiratory centre, and so rhythmic breathing ceases. During this period of apnœa, oxygen is steadily removed from the alveoli, so that two minutes later, the alveolar oxygen tension is only 30 mm. Hg. This means that a very considerable degree of oxygen lack is present. At the same time CO_2 has been passing continuously from the

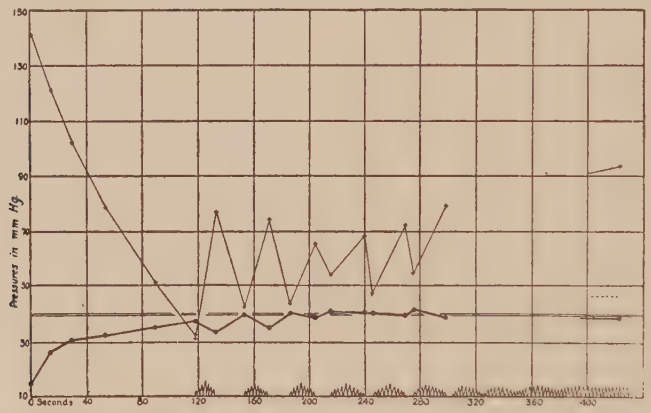

Fig. 92.—Changes in Tension of Gases in Alveolar Air and Breathing after Forced Respiration for two minutes.—Douglas and Haldane.

Upper curve, pressure of oxygen in alveolar air; Middle curve, pressure of CO_2 in alveolar air; Lower curve, respiration; Straight thick line = normal CO_2 tension (40 mm. Hg).

tissues into the venous blood, diffusing out into the alveoli and remaining there. Thus the alveolar and arterial CO_2 tension slowly rises, reaching a level of about 36 mm. Hg. This tension is still below the threshold level. In spite of this, however, great "air hunger" is experienced and the breathing is resumed.

Under normal conditions there are always adequate supplies of oxygen in the blood, and so variations in the CO_2 tension alone control the centre. Now oxygen lack is also present, and so the centre responds as soon as the CO_2 tension approaches the requisite minimal level. With resumption of the breathing, fresh oxygen is taken in, the alveolar oxygen rises and the oxygen want is temporarily relieved; at the same time, too, CO_2 is washed out from the alveoli and the arterial CO_2 tension falls. Thus both factors in the coalition of forces which brought about respiratory activity have been weakened. The breathing therefore ceases again. Similar events occur during the next period of apnœa: the alveolar oxygen is used up and increasing oxygen want develops; CO_2 accumulates and the alveolar

and arterial CO_2 rise. Breathing resumes again. This cycle is repeated several times. It may be wondered why the process does not continue indefinitely. The reason is that the brief bouts of breathing do not succeed in washing out CO_2 from the alveoli as rapidly as it is being turned out from the tissues and blood. The alveolar CO_2 is a little higher at the end of each period of apnœa than it was at the beginning, and thus gradually reaches the threshold level. But the breathing does not at once become regular. Some time must elapse before the tension of CO_2 in the respiratory *centre* itself comes into equilibrium with the arterial blood, because the surrounding lymph and the cytoplasm of the cells only gradually become saturated with CO_2 at the new partial pressure.

There is little doubt of the essential correctness of the above interpretation of the facts because of the following experiments:

1. If hyperventilation is carried out with air containing more than 5 per cent. of CO_2 so that the alveolar air cannot be lowered below the normal threshold, apnœa cannot be induced.

2. If pure oxygen instead of air is taken in during the period of forced breathing, the apnœa is greatly prolonged, and in one case persisted for

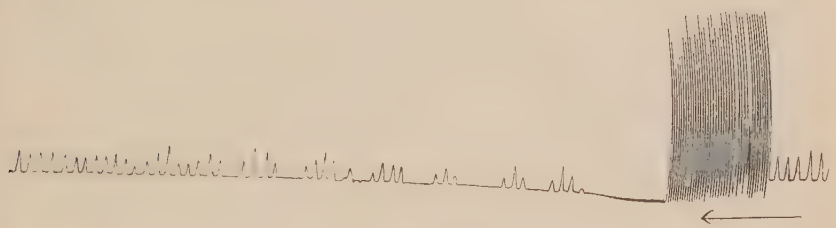

Fig. 93.—Record of Respiration in subject O. G. Tracing reads from right to left. After period of voluntary hyperpnœa, apnœa develops, followed by periodic breathing.

eight minutes. This is due to the fact that the resumption of the breathing had to await the rise of the CO_2 tension to its normal minimal value. Oxygen want does not occur, and the oxygen tension is still high at the end of the period of apnœa. The breathing recommences gently without any sign of periodicity, regular breathing being maintained when CO_2 is the effective stimulus.

Cheyne-Stokes Breathing.—This type of breathing occurs in a variety of disease conditions and is usually a symptom of considerable gravity. The pauses are longer than in the experimental form, *e.g.* up to 30 seconds or more; the breathing increases gradually to a maximum and then dies away. Cheyne-Stokes breathing is associated with a diminished cerebral circulation or with a damaged respiratory centre. (i) When the *cerebral circulation* is impaired, *e.g.* from rise of intracranial pressure (due to tumour, hæmorrhage, or abscess within the cranial cavity) or from heart failure, the respiratory centre suffers from oxygen lack, especially during sleep. (ii) In uræmia and other conditions the centre is depressed by the action of *poisons* which have accumulated in the body. Owing to the feeble state of the centre, shallow breathing results, which in its turn, because of the uneven ventilation of the lungs, produces *anoxæmia* (p. 339). The respiratory centre responds to the stimulus of oxygen lack in the usual periodic manner.

First there is an increase in the breathing which improves the oxygenation of the centre and washes out CO_2 excessively from the blood. This is followed in turn by dwindling of the breathing and apnœa. During this period CO_2 reaccumulates and oxygen lack develops once more and the breathing resumes.

The administration of oxygen to improve the nutrition of the centre, or of CO_2 to act as a respiratory stimulant, abolishes the periods and establishes regular breathing. Improvement of the cerebral circulation by treating the cardiac failure, or elimination of the toxins in renal cases, will produce more lasting benefit.

Vagi in Respiration.—Some vagal *broncho-constrictor fibres* pass to the smooth muscle of the bronchial wall. These fibres are reflexly stimulated in *asthma*. The afferent impulses producing this effect may arise from many parts of the body—*e.g.* from the nose (polypi), stomach, uterus, or from the bronchial tract itself. As a result of the spasm of the bronchial wall, the lumen is diminished. Inspiration, which is an active movement, can overcome the obstruction, and succeeds in drawing air into the lungs. Expiration is purely or mainly passive, so there is considerable difficulty in expelling air from the lungs.

Afferent fibres arise in the walls of the alveoli of the lung and in the mucous membrane of the respiratory passages, and pass up to the respiratory centre in the vagus nerve. These fibres exert several effects. (i) During ordinary breathing, impulses pass up the vagus, checking the extent of inspiration and of expiration, and thus hurrying up the rate of breathing (Hering-Breuer reflex); (ii) if the lungs are excessively distended or collapsed, impulses pass to the respiratory centre to attempt to restore the lungs to the normal mean position, which is midway between distension and collapse; (iii) afferent impulses from the laryngeal mucous membrane give rise to the *cough* reflex and thus protect the respiratory passages from foreign bodies.

The following is a useful generalization: the *chemical* factors (H ion concentration, oxygen tension), control the *total pulmonary ventilation*; the afferent *vagal* impulses control the *rhythm of the breathing*.

The rôle of the vagi in respiration has been studied as follows:

1. Action of Air-Currents.—Tracheotomy is carried out and the vagi are then divided low down in the neck so that impulses can no longer pass up from the lungs but can still proceed from the upper part of the trachea. It is found that if air is blown down the larynx into the upper trachea, the downward current of air arrests inspiration. By blowing air upwards, expiration may be inhibited but less readily (Lumsden). It is suggested that downward moving air-currents, which are set up during inspiration, stimulate the sensory vagal nerve endings in the ciliated tracheal and bronchial mucous membrane, and reflexly inhibit inspiration; to a less extent, upward moving air-currents inhibit expiration. The depth of the breathing is thus reflexly kept in check.

2. Division of Vagi.—If the vagi are divided high up in the neck, breathing becomes *slow* and *deep*, as would be expected if the vagi normally check the depth of the breathing reflexly. The paralysis of the laryngeal muscles which is produced at the same time, obstructs the air-way, and this too tends to slow down the breathing. *Stimulation* of the central end of the cut vagi produces very variable results. The breathing may *cease—vagus apnœa*;

this is usually due to a prolonged inspiratory or a prolonged expiratory effort; or rapid shallow or rapid deep breathing may be set up. These experiments merely illustrate that the afferent fibres in the vagus can influence the respiratory centre in a variety of ways.

3. Action Current in the Vagi.—An action current passes up the vagi with each respiratory movement (Einthoven). During *quiet* breathing, an action current is only detected at the end of inspiration—*i.e.* inspiration being the active phase of quiet breathing, is alone checked. During *forced* breathing, two action currents pass up (*i.e.* at the end of inspiration and the end of expiration), checking both phases of the breathing.

4. Distension and Collapse of the Lungs.—i. If the lungs are forcibly distended, the first effect is a prolonged expiratory effort.[1] In other words, an attempt is made to expel the excess air and restore the lungs to their normal position. ii. If the lungs are deflated by sucking air out, a strong inspiratory effort is made for the reason given. Such degrees of distension or collapse probably never occur during normal life. The responses mentioned are *protective* ones, to guard the lungs against conditions which would tend to harm them. Excessive distension, if allowed to continue, breaks down the thin walls between adjacent alveoli and produces large bullæ. If the vagi are cut, no response is made to collapse or distension of the lungs.

5. The vagi also carry up impulses, set up by other nocuous stimuli, *e.g.* irritant gases, and produce active expiration.

6. State of the Centre.—The chemical stimulus to the respiratory centre determines to what extent inflation and deflation must occur before the vagal stimuli from the lung become effective. When air containing excess of CO_2 is breathed, or when CO_2 accumulates in the blood as a result of muscular exercise, the stimulated respiratory centre produces more extensive movements before the vagi can reflexly inhibit them, as witnessed by the deeper breathing present in these conditions. A respiratory centre which is failing from long-continued lack of oxygen, or which is less active because of lowered carbon dioxide pressure, is more easily affected by vagal inhibition, and so rapid *shallow* breathing results (Haldane) (cf. p. 372).

It might be pointed out that the nerves of deep sensibility from the thoracic wall and abdominal parietes probably convey information to the respiratory centre about the position and movements of the respiratory muscles and so aid in the regulation of respiration.

Summary.—The vagi, as the great afferent nerves of the lungs, serve to *protect* them against the effects of excessive distension or collapse or other nocuous stimuli. They *inform* the respiratory centre of movements of air-currents and the position of the lungs, and reflexly *check* the depth of the breathing to an extent which depends on the level of functional activity of the centre.

Other Factors influencing Breathing.—Breathing is influenced (i) by

[1] In animals these experiments are most conveniently carried out on the rabbit, in which there is a slip of the diaphragm passing from the vertebral column to the xiphoid; this slip has an independent nerve- and blood-supply and can be detached from the xiphoid and from the rest of the diaphragm and attached to a lever. A record of the movements of the diaphragm is thus obtained (Head). If the lungs are distended the diaphragm slip passes into the expiratory position (*i.e.* it relaxes); if the lungs are collapsed it passes into the respiratory position (*i.e.* it contracts). If the experiments are repeated after double vagotomy the rhythm of the diaphragm continues without alteration.

the *higher centres*; (ii) by *afferent impulses* from the surface of the body, *e.g.* painful or thermal stimuli; (iii) during *sleep* the respiratory centre is depressed and does not maintain an adequate pulmonary ventilation, so that the alveolar CO_2 rises considerably (Leathes); (iv) breathing is inhibited during *swallowing* (p. 401) and after the injection of *adrenaline* (p. 129).

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CARRIAGE OF OXYGEN IN THE BLOOD

Carriage of Oxygen in the Blood.—Methods—Blood gas analysis—Dissociation curve of hæmoglobin and blood—Oxygen interchanges in tissues and lungs—Coefficient of oxidation.

Anoxæmia.—Effects—Nervous system—Digestion—Circulation—Respiration—Delayed effects—Acclimatization—Types—Anoxic type—High altitudes, alteration of alveolar epithelium, partially unventilated lung—Anæmic type—Carbon monoxide poisoning—Stagnant type.

Cyanosis.—Definition—Modifying factors—Causes—Heart disease—Pulmonary disease—Altered hæmoglobin—Sulph-hæmoglobinæmia.

Certain essential figures must be noted:

Alveolar air: oxygen forms 13 to 14 per cent.; oxygen tension is about 105 mm. Hg.

Arterial blood: Oxygen tension is 100 mm. Hg (*i.e.* 5 mm. Hg less than in alveolar air); amount of oxygen is 18·5 c.cm. per 100 c.cm. blood (in the case of blood containing about 14 grm. Hb per 100 c.cm.).

Venous blood: Oxygen tension is 40 mm. Hg (65 mm. Hg lower than in alveolar air); amount of oxygen, at rest, is 15 c.cm. per 100 c.cm. blood.

In severe exercise the oxygen content of the venous blood falls and may be as low as 3·5 c.cm. per 100 c.cm. blood.

The amount of O_2 which can be held in simple solution in the plasma at a tension of 100 mm. Hg is 0·30 c.cm. As the actual amount found in the arterial blood is 18·5 c.cm. per cent., it is clear that most of the oxygen is carried in chemical combination. Owing to the great resemblance between the behaviour of blood and a solution of hæmoglobin, it is believed that oxygen is carried in loose combination with hæmoglobin.

It is important to determine the amount of oxygen which hæmoglobin solutions or whole blood take up at different tensions of oxygen. To study this problem it is first necessary to expose a series of small samples of blood (*e.g.* 3 c.cm.) in a glass vessel (of about 400 c.cm. capacity) called a *tonometer* to various gas mixtures containing a known percentage of O_2 and therefore with a known O_2 tension. The bottle is rotated in a bath for half an hour. The blood spreads out as a thin film over the sides of the bottle and comes into equilibrium with the gas and finally contains O_2 at the tension present in the tonometer.

The *amount* of oxygen taken up by the blood must next be determined by means of Haldane's *blood-gas analysis* apparatus. A measured amount of the blood (2 c.cm.) is introduced into a small bottle under cover of 2 c.cm. of a 1 per cent. Na_2CO_3 solution, which fixes all the CO_2 in solution to form $NaHCO_3$. It is connected up with a graduated tube of narrow bore, and the taps are closed ; the blood is shaken for a few minutes, takes up O_2 from the air in the apparatus until it is fully saturated ; and the amount of O_2 absorbed is noted. A little saponin is added to lake the blood. The solution then becomes clear instead of being opaque as heretofore. 0·25 c.cm. freshly prepared potassium ferricyanide $K_3Fe(CN)_6$ is added. All the oxygen in combination with the hæmoglobin is liberated, and the amount given off is measured. This is called the *oxygen capacity* of the blood. It should be noted that $K_3Fe(CN)_6$ cannot penetrate into the interior of the red corpuscles and therefore the blood must be thoroughly laked beforehand. Methæmoglobin is left behind in the bottle, as the reduced hæmoglobin formed takes up oxygen from the reagents in the solution as follows :

$$HbO_2 + K_3Fe(CN)_6 + NaHCO_3 \longrightarrow \underset{\text{(Methæmoglobin.)}}{HbO} + 2K_3NaFe(CN)_6 + 2CO_2 + H_2O + O_2$$

Suppose the amount of oxygen necessary to saturate the blood was 13 c.cm. per cent. (first estimation) and the oxygen capacity was 20 c.cm. per cent. (second estimation). The oxygen *content, i.e.* the amount of oxygen originally present in the sample, was 20 minus 13=7 c.cm. per cent.

$$\text{The ratio } \frac{\text{oxygen content}}{\text{oxygen capacity}} = \frac{7}{20} = 35 \text{ per cent.}$$

represents the *percentage saturation* of the original sample with oxygen.

In this manner a *dissociation curve* may be plotted showing the relation between the partial pressure of oxygen (abscissa) and the percentage saturation of the blood or hæmoglobin with oxygen (ordinate). It should be remembered that 100 per cent. saturation represents an oxygen capacity of about 19 to 20 c.cm. per cent. The actual figure differs in different individuals according to the concentration of hæmoglobin in their blood (p. 195). A consideration of this curve reveals many points of interest (Fig. 94).

At the oxygen tension of the arterial blood (100 mm.) a simple hæmoglobin solution becomes almost fully saturated with oxygen (about 95 or 96 per cent. saturated). At the oxgyen tension in the mixed venous blood, *i.e.* 40 mm. Hg, hæmoglobin is still combined with most of its oxygen. In other words, if our blood consisted of a simple hæmoglobin solution, when it passed through the tissues, very little oxygen would be evolved and death from asphyxia would result. The curve for hæmoglobin is a rectangular hyperbola ; that for blood under the conditions found in the body is S-shaped. It is almost fully saturated at 100 mm. O_2 tension, taking up about 18·5 c.cm. O_2 per cent. But at a tension of 40 mm. it only carries about 15 c.cm. O_2 per cent., *i.e.* 3·5 c.cm. per cent. have been made available for use by the tissues. It should be carefully noted that at tensions below 40 mm. the curve descends very steeply. This means that if the oxygen tension falls below 40 mm., *e.g.* to 30 mm. as in severe exercise, blood gives off about 70 per cent. of its contained oxygen (*i.e.* about 14 c.cm. per cent.), and greatly increased quantities of oxygen are supplied to the tissues.

The discrepancy between the behaviour of a simple hæmoglobin solution and whole blood is explained by the fact that blood in the body is at a temperature of 37° C.; contains CO_2 at a tension of 40 mm. Hg, and inorganic salts (of which the most important is the potassium in the corpuscles); and has a high concentration of hæmoglobin in the corpuscles.

1. By raising the CO_2 tension to which a simple hæmoglobin solution is exposed, the dissociation curve is "shifted to the right" *i.e.* the convexity of the curve is flattened, which means that more oxygen is evolved at low oxygen tensions. CO_2 acts by altering the H ion concentration of the

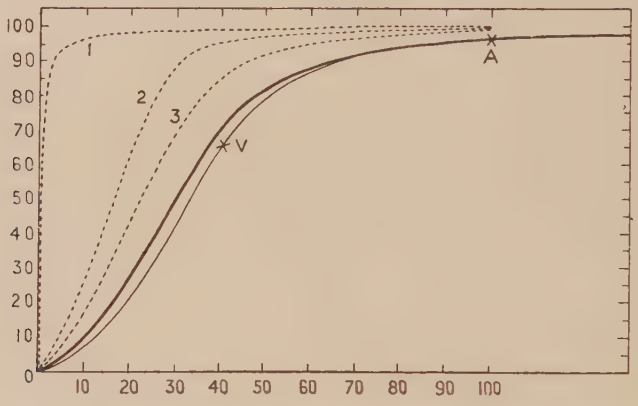

FIG. 94.—Diagram to illustrate the Behaviour of Solutions of Hæmoglobin and of Blood under Different Conditions.

Abscissa: Tension of Oxygen in mm. Hg. Ordinate: Percentage saturation of hæmoglobin with oxygen.
Dotted lines: Hæmoglobin solutions—1, Room temperature and no CO_2 tension; 2, Body temperature and no CO_2 tension; 3, Body temperature and 20 mm. CO_2 tension.—After BARCROFT.
Continuous lines: Blood. Thick line—In presence of constant pressure of 40 mm. CO_2. Thin line—Dissociation curve in body when disappearance of oxygen is accompanied by increase of CO_2 pressure which facilitates dissociation of oxyhæmoglobin.—After HALDANE.
A = Arterial point; V. = Venous point.

solution. If the cH is raised by any other acid, *e.g.* lactic acid, similar effects are produced.

2. Raising the temperature to that of the body, *i.e.* 37° C., has a similar, though slight effect.

3. The addition of salts in appropriate concentration makes the curve more S-shaped under certain conditions.

4. The strength of the hæmoglobin solution employed is of importance. A weak solution (*e.g.* 1 : 500) always gives a hyperbolic curve even in the presence of salts, and whether the reaction is acid, alkaline, or neutral. The strongest hæmoglobin solution that can be obtained gives an S-shaped curve under all circumstances. It is only in medium solutions that the presence of salts gives an S-shaped curve. It is noteworthy that the concentration of hæmoglobin reaches its maximum in the red blood corpuscles (about 30 grm. Hb per 100 c.cm. of corpuscles), and that is presumably one of the chief factors producing the S-shaped dissociation curve of blood.

If the CO_2 tension, temperature, and salt content and hæmoglobin concentration are adjusted to that of the body, the solution behaves like blood.

Venous blood always contains CO_2 at a higher tension than arterial blood (46 mm. at rest). The dissociation curve for reduced blood is consequently shifted somewhat to the right compared with that for arterial blood.

So far we have considered the *extent* of dissociation of oxyhæmoglobin at various oxygen tensions. The *rate* of dissociation must also be considered.

1. To obtain the rate of *reduction*, fully oxygenated blood is placed in a tube, and hydrogen is bubbled slowly through it to drive off the oxygen. Samples of the blood are examined at intervals to determine their percentage saturation.

2. To obtain the rate of *oxidation*, reduced blood is employed, and a mixture of N_2 and O_2 (O_2 at 100 mm. Hg tension) is slowly bubbled through it until oxygenation is completed. The results in both cases are plotted in

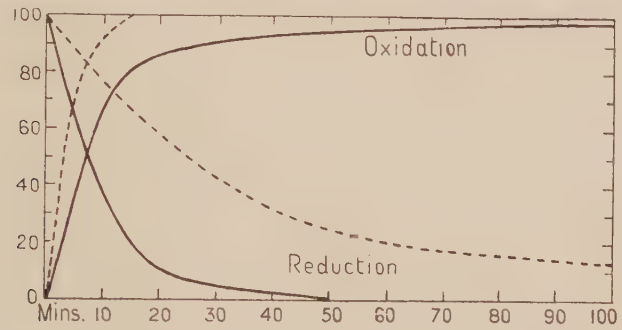

FIG. 95.—Curves showing Relative Rates of Oxidation and Reduction of Blood as influenced by Temperature and CO_2 Tension.

Abscissa : Time in minutes. Ordinate : Percentage saturation with oxygen.
Dotted lines : At room temperature and no CO_2 tension.
Thick lines : At body temperature and 40 mm. CO_2 tension.—After BARCROFT.

the form of a curve. The time in minutes is shown along the abscissa and the percentage saturation along the ordinate (Fig. 95).

At room temperature the rate of oxidation is very rapid (88 per cent. saturation in 10 minutes, 95 per cent. saturation in 15 minutes). The rate of reduction, however, is very slow at low temperatures (60 per cent. saturated after 15 minutes). If the CO_2 tension is raised to 40 mm. Hg, oxidation is slightly retarded but reduction is accelerated. If the temperature is raised to 37° C. the rate of oxidation is probably unaffected, but that of reduction is greatly speeded up. The oxidation and reduction curves now correspond very closely, *i.e.*, under body conditions the rate of taking up and giving off oxygen is about the same.

The *extent* of dissociation depends therefore on (i) oxygen tension ; (ii) CO_2 tension (and H ion concentration) ; (iii) electrolyte content ; (iv) temperature ; (v) concentration of hæmoglobin.

The *rate* of dissociation depends on : (i) CO_2 tension ; (ii) temperature.

Oxygen Carriage in the Body.—1. Arterial blood passes to the tissues carrying about 0·3 c.cm. of oxygen in solution, and about 18 c.cm.

in combination with hæmoglobin. The tension of the gas is 100 mm. Hg, and it must be remembered that tension is a property solely of the oxygen in *solution*. The oxygen tension in the muscles is estimated to be 20 mm. Hg at rest. Owing to the great difference of oxygen pressure, oxygen rapidly passes out of the plasma through the capillary wall and tissue fluid to reach the tissue cells. The oxygen tension in the blood falls to about 40 mm. Hg; complete equilibrium with the tissues is not achieved. The oxyhæmoglobin in the corpuscles is now exposed to a tension of 40 mm. Hg in the plasma around it, and therefore cannot retain all the oxygen it has hitherto held in combination. Dissociation occurs, and about 3·5 c.cm. oxygen per cent. are liberated. This amount of gas cannot remain in solution in the plasma, which already holds as much as it can; the oxygen liberated from the corpuscles must therefore diffuse out into the tissue fluid.

As a result, the venous blood leaves with an oxygen tension of 40 mm. Hg and an oxygen content of 15 c.cm. per cent. There is slightly less oxygen in solution, and considerably less oxygen in combination with hæmoglobin. The *arterial-venous oxygen difference* or difference in oxygen content of arterial and venous blood is 18·5 minus 15=3·5 c.cm. per cent.

The *coefficient of utilization*

$$= \frac{O_2 \text{ taken up by tissues}}{O_2 \text{ content of arterial blood}} = \frac{3{\cdot}5}{18{\cdot}5} = 0{\cdot}19, \text{ or } 19 \text{ per cent.}$$

2. When a tissue is active, *e.g.* the skeletal muscles during vigorous muscular exercise, the number of capillaries which allow the passage of blood through them becomes greatly increased (*e.g.* 40 times), and all the capillaries become widely dilated. Owing to the greatly increased cross-section of the vascular bed locally, the rate of flow of blood through the tissue is slowed down, and more time is available for dissociation and diffusion of oxygen. A large surface of blood is in contact with the tissues, and the gaseous interchange is further facilitated. The tissue is consuming O_2 at a great rate, and so the oxygen tension within it probably falls to zero. A very steep oxygen pressure gradient exists between plasma and tissues, permitting rapid diffusion. The oxygen tension in the blood falls, *e.g.* to 30 mm. Hg; the oxyhæmoglobin dissociates and gives off about 60 per cent. of the oxygen combined with it. In an active tissue the temperature rises, larger amounts of CO_2 are evolved, and the H ion concentration tends to go up. The rise of temperature and CO_2 tension increase the rate of dissociation of HbO_2. The increased CO_2 tension means that HbO_2 gives off more oxygen at any given oxygen tension. At 30 mm. Hg O_2 tension *arterial* blood gives off half its combined oxygen; *venous* blood—in which the disappearance of O_2 is accompanied by an increase of CO_2 pressure—gives off 58 per cent. of its oxygen (see Fig. 94). It is possible that very active muscles may abstract almost all the oxygen brought to them in the arterial blood, and the blood leaves the muscles almost completely reduced. The mixed venous blood (*i.e.* the blood in the right auricle) may have an oxygen content as low as 7 or 8 c.cm. in strenuous exertion. The arterial venous oxygen difference is 18·5 - 8=10·5 c.cm. per cent., and the coefficient of utilization is $\frac{10{\cdot}5}{18{\cdot}5}$=54 per cent. In very vigorous exertion (*e.g.* running a

quarter-mile race) the mixed venous blood may only contain about 3·5 c.cm. oxygen per cent.; the arterial venous oxygen difference is 18·5 – 3·5 = 15 c.cm. per cent., and the coefficient of utilization is $\frac{15}{18{\cdot}5} = 81$ per cent.

Activity of a tissue, by altering the calibre and number of the capillaries and changing the local O_2 and CO_2 tension and the temperature, thus enables *four* times the amount of oxygen to be abstracted from the *same* amount of blood-flow compared with the resting utilization

3. When the mixed venous blood (O_2 tension 40 mm.) passes through the lungs it is exposed to an oxygen tension in the alveoli of 105 mm. Hg. Owing to the great difference of oxygen pressure, the gas rapidly diffuses from the alveoli through the thin pulmonary and capillary epithelium into the plasma. The amount of oxygen in solution is increased, and the tension rises to 100 mm. Hg. The hæmoglobin exposed to this high oxygen pressure takes up oxygen from the surrounding plasma and unites with it chemically. As oxygen is thus removed from the plasma, fresh amounts of oxygen can pass from the lungs into the blood. A constant stream of oxygen thus passes from the lungs into the plasma and thence into combination with hæmoglobin. The arterial blood finally leaves the lungs almost fully saturated with oxygen (95 per cent. saturated), at an oxygen tension of 100 mm. Hg. The oxygen content is then about 18·5 c.cm. (the exact figure depending on the hæmoglobin content of the blood), of which only 0·3 c.cm. is in solution.

Coefficient of Oxidation.—The quantity of oxygen used by different tissues varies not only with their degree of activity, but also with the nature of the tissues. The *coefficient of oxidation* is the amount of oxygen in cubic centimetres used by an organ or tissue per gramme per minute (Barcroft). To obtain this coefficient the following facts must be determined: (i) the blood-flow through the organ; (ii) the oxygen content of the blood entering, and of the blood leaving, the organ; (iii) the weight of the organ.

(*a*) In the case of glands (submaxillary, pancreas, kidney), the coefficient at rest, or when activity is at a minimum, is 0·03 c.cm. During vigorous secretory activity it rises to 0·1 c.cm. The figure for the non-stimulated suprarenal gland is 0·045 c.cm.

(*b*) Voluntary muscle when it is toneless (nerves cut) has a coefficient of 0·003 c.cm.; when tone is present, 0·006 c.cm.; during gentle contraction, 0·02 c.cm.; during violent activity, 0·08 c.cm. In heart muscle when contractions are feeble and slow the coefficient is 0·007 c.cm.; during great activity it is 0·08 c.cm. In unstriped muscle the coefficient at rest is 0·004 c.cm., and during contraction 0·007 c.cm.

ANOXÆMIA

This term has been introduced to denote lowered oxygen content of the blood. Anoxæmia occurs much more commonly than has hitherto been suspected, and complicates many diseases as a secondary factor. It is important to obtain a clear idea of the effects of anoxæmia and the various conditions which may produce it.

Effects of Anoxæmia.—1. Nervous System.—When anoxæmia is of very rapid onset, loss of consciousness may occur without any warning;

as when a miner puts his head into a cavity full of methane gas and drops as though felled by a blow. When he recovers on breathing pure fresh air for a few seconds, he really believes that he has been knocked down, and acts accordingly, assaulting any one in his vicinity. If anoxæmia develops more gradually, the intellect and the senses become dulled without the person being subjectively aware of what has happened. When the anoxæmia is relieved, the sudden increase in the power or in visual acuity comes as a great surprise (cf. p. 239).

Symptoms similar to those resulting from an overdose of alcohol may be present. Headache, depression, apathy, and drowsiness; or excitement and general loss of self-control. The subject will sing and shout, or burst into tears for no apparent reason. He may be extremely quarrelsome or insolent. If in any danger, he may refuse to take such measures as are obviously essential for his safety. He feels quite confident that his mind is clear and that his judgment is sound, in spite of his dangerous behaviour. Memory is impaired and appreciation of time is altered. He may think he has gone quite a long way when he has only stumbled a few yards.

The experiences of Haldane and Kellas in a pressure chamber, in which the barometric pressure was only 320 mm. Hg, are very interesting. Haldane found he could no longer write or make any observations, and so he handed the notebook to Kellas, who, as an experienced mountaineer, was better acclimatized. For the next $1\frac{1}{4}$ hours Haldane insisted that the pressure be kept at the low level, but could remember nothing of this later. At last he consented to having the pressure raised to 356 mm., and picked up the mirror to look at his lips. Kellas noticed that for a long time he peered at the *back* of the mirror. As the anoxæmia was relieved, Haldane realized he had been longer in the chamber than he had originally intended, and raised the pressure to 450 mm. He then noticed the feeling and power return to his legs.

Understanding is impaired more than sensation; the subject sees without knowing what he is looking at. He finds it difficult to understand printed or written words. Pain is dulled: a miner poisoned with CO gas readily burns himself with his lamp. Finally, each sense is lost suddenly, hearing being retained longest.

The subject misjudges the position of things and cannot walk straight. The inco-ordination in walking is succeeded by sudden loss of power in the legs, and collapse occurs; paralysis of the arms follows rapidly. This occurred in a balloon ascent to 29,000 feet in 1862, when Glaisher was completely paralysed and Coxwell only retained movement in his head. He grasped the valve rope with his teeth, and so stopped the ascent and saved the lives of the party. In another case, one airman was completely paralysed before he could put the oxygen tube to his lips, and Tissandier alone survived. These experiences illustrate vividly the acuteness with which paralysis sets in, and the recklessness displayed by men in rarefied atmospheres. Similarly, in colliery explosions, rescuers become paralysed when they have gone too far into the poisonous atmosphere to be rescued by others. It is possible that many of the psychical abnormalities that occur in severe cardio-respiratory disease are largely attributable to anoxæmia.

There is great muscular weakness and easy fatiguability. Progress is

made with extreme slowness. The mountaineer "may think twice before turning over in bed."

2. Digestion.—There is nausea, loss of appetite, and vomiting. At 26,700 feet, the members of the Everest Expedition could with difficulty bring themselves to eat meat at all. Chocolates and biscuits were consumed as a duty, and only soup and coffee were taken with relish. (On the mountain-side, great thirst was a striking feature because of the marked loss of body fluid in the dry cold air.)

3. Circulation.—There is at first an increase in the frequency and in the apparent force of the heart beat. A rise of blood pressure may occur. These results are due to anoxæmia stimulating the vasomotor and cardio-accelerator centres in the medulla. The blood is thus kept out of the splanchnic area and skin and made available for the essential parts of the body, and made greater use of by being sent round more rapidly. Later the force of the heart dies down, though the frequency may increase further. In the Everest expedition the pulse-rate during motion was 160 to 180 per minute or even more, of good volume and regular. All the men who went above 27,000 feet developed dilated hearts, which were restored to normal in 1 to 3 weeks. Owing to the imperfect oxygenation of the blood, cyanosis develops (for full discussion see p. 343). According to the amount of blood in the capillaries, the mucous membranes may appear black or leaden grey.

Respiration.—The effects on the breathing have already been fully considered (p. 323). The breathing is increased in rate, but tends to be shallow and periodic in character.

It is found that very trifling changes in the environment may make a great difference to the affected person. Thus, in the anoxæmia of CO poisoning, bringing the patient out into the cool fresh air may cause loss of consciousness. Climbers find that under certain conditions of wind or temperature they are more disabled. The importance of attending to the minutiæ of nursing comfort in the case of anoxæmic patients is obvious.

Delayed Effects. — Beside the immediate results of anoxæmia, numerous *delayed* effects appear, depending on the length and severity of the exposure. An inspector of mines who had been in poisonous atmospheres, on returning to the surface, first shook hands cordially with all the bystanders. The doctor offered him his arm, which he regarded as an insult, and there and then took off his coat and challenged him to fight. Mountain sickness with typical nausea, and vomiting and depression, may ensue 8 to 12 hours after the exposure; perhaps even after the descent. A slight degree of oxygen lack may therefore act insidiously and only reveal its effects after a long latent period. This conclusion is of importance when we consider that mild anoxæmia is fairly common clinically. Following prolonged exposure to severe oxygen lack, very formidable after-effects occur. "Anoxæmia not only stops the machine but wrecks the machinery" (Haldane).

In CO poisoning, consciousness may not be regained for many hours after the condition of the blood has been restored to normal; or coma may endure and pass into death. Convulsions may occur at intervals owing to injury to nervous elements, and paralyses of various sorts may follow. The mental condition may be temporarily impaired or the subject may pass into a state of

dementia. Pneumonia may set in after a day or two, and this is an index of the generally precarious condition of the whole body.

Acclimatization.—Given a slow onset of anoxæmia and favourable circumstances, the various compensatory activities of the body are brought into play. At moderate heights, the early unpleasant symptoms may pass away completely. At Pike's Peak (14,100 feet), the general discomfort, the fatigue, and the periodic breathing passed off in 10 days, and all the subjects felt and looked extremely well. Similarly, in the anoxæmia of disease we may expect to find the symptoms masked for a long time, only to be strikingly displayed when compensation breaks down.

Acclimatization is effected as follows :

1. The *kidney* begins to excrete urine of an alkaline reaction and with a low NH_4 content, and the alkalæmia is thus compensated. The pulmonary *ventilation* is thus permitted to proceed at a sufficient level to maintain a much higher alveolar oxygen tension than otherwise would have been the case.

2. The oxygen-carrying capacity of each unit of blood is increased. At first, the spleen may contract and discharge its contained red blood corpuscles into the circulation (p. 213). Then the red marrow proliferates and the red count per c.mm. is raised, and the hæmoglobin index may reach 115 to 150 per cent. ; many immature cells (reticulocytes) are found in the circulating blood.

3. The lung volume is said to increase ; the alveolar epithelium is thus thinned and allows gaseous exchanges to occur more rapidly. According to Haldane, actual *secretion* of oxygen may occur into the blood by means of the pulmonary epithelium, so that the oxygen tension in the arterial blood may be higher than in the alveolar air ; but, as previously pointed out (p. 314) this has not been confirmed.

Types of Anoxæmia.—Three types of anoxæmia may be recognized (Barcroft) :

1. *Anoxic type* : where the *tension* of oxygen in the arterial blood is lower than normal, and consequently the hæmoglobin is not saturated with oxygen to the normal extent.

2. *Anæmic type* : the oxygen tension in the arterial blood is normal, but the quantity of *functioning hæmoglobin* is too small.

3. *Stagnant type* : the arterial blood is normal in oxygen tension and oxygen content, but it is supplied to the tissues in insufficient amounts.

We may now discuss each form more fully.

1. Anoxic Type.—This form of anoxæmia occurs characteristically at high altitudes. The tension of oxygen in the alveolar air is too low ; as the arterial blood is usually in equilibrium with the alveolar air, the tension of oxygen in the blood is too low. This form of anoxæmia is very serious.

i. The goal of the breathing is to maintain an adequate oxygen *tension* in the arterial blood, in the same way as it strives to maintain a normal CO_2 tension. If the oxygen tension in the blood falls, breathing is stimulated and results (as already explained) in washing out of CO_2 from the blood. It will be remembered that the process of giving up oxygen from oxyhæmoglobin is greatly influenced, both as to extent and rate, by the CO_2 tension. If the latter falls, oxyhæmoglobin tends to retain its oxygen, and so the tissues are starved of oxygen independently of the amount present in the blood.

ii. There is good reason to believe that the *velocity* of the oxidative processes in the tissues is proportional to the *pressure* head at which oxygen is supplied. To use a very inexact analogy, the mud can be washed off a car more successfully with a powerful thin jet of water than with larger quantities of water sluiced over it gently. We must pay greater attention, then, to the partial pressure of oxygen in the blood than to the actual amount present.

To summarize : The tissues are hampered in three ways :

(1) The tension of oxygen in the blood is low, and so the rate of oxidation is diminished.

(2) There is less oxygen present in the blood, so that any activity demanding a large oxygen consumption is impossible.

(3) The oxygen which is present in the blood is not readily available to the tissues, owing to the low CO_2 tension hampering the dissociation of oxyhæmoglobin.

Barcroft illustrated this very well in his experiment in a respiration chamber where he was exposed to low oxygen tensions. Normally his oxygen capacity is 17·8 c.cm. per cent., his hæmoglobin is 96 per cent. saturated, and his oxygen content is 16·9 c.cm. per cent. At low oxygen tensions his hæmoglobin content rose and his oxygen capacity became 20·1 c.cm. per cent. The hæmoglobin was now 84 per cent. saturated and the oxygen content was again 16·9 c.cm. per cent. Although the *amount* of oxygen present in his blood was the same as normal, severe symptoms were present in the respiration chamber (headache, vomiting), because the oxygen *tension* was subnormal.

The *clinical* causes of anoxic anoxæmia are as follows :

Alteration of the Alveolar Epithelium.—If the walls of the alveoli are swollen and œdematous, or covered by a layer of fibrinous exudate, diffusion of oxygen into the blood cannot readily occur. The arterial blood does not attain the same oxygen tension as the alveolar air and is therefore under-saturated. This was well seen in the war as a result of poisoning with various irritant gases like chlorine. The alveoli became inflamed and sodden with fluid, and cyanosis was present in spite of deep breathing. Administration of oxygen improved the colour and the general condition of the patient, because at the higher alveolar oxygen tension the gas diffused more rapidly into the blood. In heart failure with œdema of the lungs, anoxæmia is caused in the same way.

Partially Unventilated Areas of Lung.—(1) *Shallow Breathing.*—It must be remembered that the various regions of the lungs do not open out equally and simultaneously during inspiration, but part by part, " like a lady's fan " (Keith). The alveoli nearest the moving parts of the chest wall and the diaphragm expand first, and to the greatest extent; the other regions follow suit later, and to a less extent. In shallow rapid breathing certain parts of the lungs are well opened up, and because of the frequency of the breathing receive more than their normal amount of fresh air. The alveolar CO_2 in these regions falls, and consequently a greater amount of CO_2 is washed out from the blood. Similarly, the oxygen percentage in these alveoli may rise to 16 or 18 per cent., but this is of practically no value to the blood. Arterial blood is about 95 per cent. saturated at the usual alveolar oxygen tension, and takes up a negligible additional amount of oxygen if the pressure is raised. Many parts of the lung, however, are considerably under-

ventilated, as the breathing is not deep enough or prolonged enough for them to be opened up. Less CO_2 is given off in these areas. Because of the low oxygen tension in these alveoli the blood leaves them considerably under-saturated with oxygen. If the total alveolar ventilation is normal, the CO_2 is eliminated in adequate amounts ; but not enough additional oxygen is taken up in the over-ventilated alveoli to compensate for the incomplete saturation which occurs in the under-ventilated alveoli. As a result, the blood which leaves the lungs is deficient in oxygen.

In so far as anoxæmia produces frequent shallow breathing, it tends to set up a vicious circle which tends to aggravate the original condition.

(*a*) In *neurasthenia*, after *gassing*, or *shell-shock*, a habit of frequent shallow breathing may be set up, which causes anoxæmia in the manner described and may be the cause of some of the symptoms in these conditions. The patients may be greatly improved if taught to breathe correctly.

(*b*) In fatigue of the respiratory centre in *surgical shock*, or from the depressant action of the toxins of *influenza* or *pneumonia*, shallow breathing may occur, with its usual effects.

(2) In *emphysema*, some of the alveoli are greatly distended with air, but there is no reason to think that these alveoli receive the major part of the available blood. Pathological considerations suggest quite the reverse : the blood vessels are obliterated between the most distended alveoli, so that these will receive less blood than the relatively under-ventilated alveoli. In *bronchitis*, especially capillary bronchitis, and in *asthma*, certain alveoli are partially collapsed, and the blood reaching them leaves under-arterialized.

(3) In *lobar pneumonia*, anoxæmia may be present from the vicious action of the toxin on the respiratory centre causing shallow breathing. The depth of the breathing is also restrained by the pain due to the associated pleurisy. If the blood vessels supplying the consolidated parts are obstructed, all the blood must pass through the functioning parts of the lung and there be arterialized to a certain extent. If the blood vessels of the pneumonic area are patent, the blood circulates through this region unchanged and leaves it in just as venous a state as that in which it arrived. The " arterial " blood is thus a mixture of oxygenated and unoxygenated blood. If *œdema* of the lung is present too from heart failure, the condition is still further aggravated. The percentage saturation of the arterial blood with oxygen falls from the normal 95 per cent., and figures as low as 42 per cent. have been recorded. When the percentage saturation falls below 70 per cent. the case usually ends fatally.

In *collapse* of a lobe of the lung, the same considerations will apply. In collapse due to hydro- or pneumo-thorax the blood vessels of the affected part tend to be compressed too, cutting off the blood supply of the collapsed areas.

Abnormalities of Heart and Blood Vessels.—If the blood is shunted from the right to the left side of the heart, *i.e.* through a patent foramen ovale or patent interventricular septum, part of the blood in the arteries has never passed through the lungs at all, and anoxæmia is present. Here again the " arterial " blood is a mixture of oxygenated and unoxygenated blood.

2. Anæmic Type.—This is less serious in its effects than the anoxic form. The oxygen tension in the blood is normal, so the rate of tissue oxida-

tion is maintained at its usual level. No increase in the pulmonary ventilation occurs, illustrating the relative indifference of the respiratory centre to the *amount* of oxygen in the blood, so long as the appropriate tension is maintained. At rest, the prejudicial effect on the tissues is relatively slight. Of the 18·5 c.cm. of oxygen normally contained in arterial blood, only 3·5 c.cm. are used up under resting conditions. A person with 50 per cent. hæmoglobin carries 9·25 c.cm. oxygen per 100 c.cm. blood, and so his resting requirements are readily satisfied. His capacity to do work is greatly diminished because he has not the reserves of oxygen in the blood to call upon.

(1) According to Lorrain Smith, in *chlorosis* and the anæmia of *ankylostomiasis* the blood volume is *increased*; though the hæmoglobin content per unit of blood is diminished, the total amount of hæmoglobin in the body is about the normal. In the severe anæmias—e.g. *pernicious anæmia*, *leukæmia*—the total hæmoglobin content of the blood is reduced. In exercise the sole method which is available in these subjects for increasing the oxygen supplies to the tissues is to increase the circulation rate. Acceleration of the pulse consequently occurs after slight exertion.

(2) In poisoning with the *nitrites*, nitric-oxide-hæmoglobin and some methæmoglobin are formed. With large doses of *chlorates*, methæmoglobin is formed. Marked cyanosis may be present, owing to the presence in the blood of the coffee-coloured methæmoglobin. The patient may, however, feel quite well, because the arterial oxygen tension is normal.

If an animal in this condition is kept in an atmosphere of oxygen for a sufficiently long period, the methæmoglobin gradually disappears from the blood and recovery occurs. Outside the body methæmoglobin can be converted by reducing agents (*e.g.* ammonium sulphide) into reduced hæmoglobin. It is suggested that a reducing agent is present in the blood, possibly in the red cells, which exerts a similar action inside the body. Thus a struggle goes on between the poison which is striving to form methæmoglobin and the reducing agent in the blood which endeavours to reconvert it into reduced hæmoglobin (which can then unite with oxygen). If death does not occur, methæmoglobin is partly excreted and the reducing agent gets the upper hand, thus restoring the oxygen-carrying capacity of the blood.

(3) *Carbon monoxide poisoning* needs special consideration. It is a method commonly employed by intending suicides, and occurs accidentally from escapes of lighting gas, fires, and underground explosions.

CO acts solely by displacing oxygen from its combination with hæmoglobin, forming a stable compound which is useless for gas-carrying purposes. It has no specific action on the tissues of the body, and is only poisonous because we are so dependent on functioning hæmoglobin for oxygen transport. A cockroach, whose blood contains no hæmoglobin, can be kept alive in an atmosphere containing 80 per cent. CO and 20 per cent. O_2. If a mouse is placed in a glass vessel and exposed to two atmospheres pressure of oxygen and one atmosphere of CO, it is found that almost all the hæmoglobin combines with CO, and yet the mouse remains normal while at rest and only seems to tire easily when climbing up the sides of the jar. At the oxygen pressure of the experiment, about 4·2 c.cm. per cent. O_2 are present in free solution in the plasma, and this is sufficient to supply the resting requirements of the body (Haldane).

The affinity of carbon monoxide for hæmoglobin is about 300 times as great as that of oxygen. If the normal 14 per cent. oxygen is present in the alveoli and 0·047 per cent. CO, the hæmoglobin of the blood shares itself out equally between the two gases. [Minute amounts of CO, if constantly maintained in the alveoli, can thus produce serious effects.] The symptoms then present are very serious. The subject cannot walk any distance, and sometimes can scarcely rise from his chair without collapsing on to the ground. When over 50 per cent. of the hæmoglobin is thrown out of action the slightest exertion may cause fainting. In fatal cases the percentage saturation of the blood with CO is usually over 80 per cent., but may not exceed 60 per cent. The symptoms of CO poisoning are clearly those of oxygen lack. It is noteworthy that though dizziness, faintness, and mental disturbances are present because of the cerebral anoxæmia, yet there is no appreciable increase in breathing and no "air-hunger," because the oxygen tension in the blood is normal.

It is important to consider why the symptoms are so severe when 50 per cent. of the hæmoglobin is not functioning as a result of combination with CO, and why they are relatively so mild when the hæmoglobin is reduced to the same extent in anæmia. It is found that the presence of COHb alters the dissociation curve of the functioning hæmoglobin which is still present. The curve is shifted to the *left*, and the S-shape disappears : in other words, hæmoglobin will now only give off oxygen in appreciable amounts when the oxygen tension is very low. COHb thus *prevents* adequate amounts of oxygen being given off to the tissues, which accordingly suffer very seriously.

If the patient is exposed to high pressures of oxygen (especially if CO_2 as well is added to the inspired air to stimulate the respiratory centre), CO is gradually displaced from its union with hæmoglobin by the mass action of the excess oxygen, and a normal state of the blood is gradually restored.

3. Stagnant Type.—This occurs when the circulation rate is diminished because of *heart failure* or of *impaired venous return* as in *shock* (p. 299). The tension of oxygen in the blood is normal, but the amount reaching the tissues is inadequate. The rate of oxidation in the tissues is normal, because oxygen is supplied at a high pressure head. As the blood circulates more slowly in the tissues there is more time available for reduction of oxyhæmoglobin. Furthermore, the impaired circulation causes CO_2 accumulation in the tissues, which facilitates the giving off of oxygen. Thus the tissues make the most effective use of what oxygen does reach them in the blood.

The following table (from Barcroft) indicates the relative prejudice produced by an equal degree of oxygen lack of the different types :

	O_2 in Blood going to Vessels of Tissues.	O_2 reaching Tissues
Normal . .	100 (say).	100 (say).
Anoxic . .	66 ('.' of under-arterialization).	42
Anæmic . .	66 ('.' of diminished Hb).	66
Stagnant . .	66 ('.' of diminished circulation).	75

The table shows how the high CO_2 tension and slow flow in the stagnant form help the giving off of oxygen; and how the low CO_2 pressure and low oxygen tension aggravate the oxygen deprivation of the tissues in the anoxic form.

CYANOSIS

Definition.—By cyanosis is meant a blue or bluish colour of the skin, mucous membranes, or the deeper organs. It may be general in distribution, but is usually more marked in certain regions. It is most often localized in the lips, nose, cheeks, ears, hands, and feet.

Cyanosis is due to a change in the character of the circulating blood, and so it disappears if the blood is squeezed out from the part. In the work on cyanosis it is customary to assume that 100 c.cm. blood have an oxygen capacity of 20 c.cm. As 1 grm. of hæmoglobin combines with 1·34 c.cm. oxygen, there is assumed to be a hæmoglobin concentration of $\frac{20}{1{\cdot}34}$ = 15 grm. per 100 c.cm. blood.

Cyanosis depends on the *absolute amount of reduced hæmoglobin present* in the blood (occasionally it is due to the presence of met- or sulph-hæmoglobin, p. 346); the amount of oxygenated hæmoglobin present is of little importance. The amount of reduced hæmoglobin in blood can be expressed as volumes per cent. of oxygen *unsaturation, e.g.* 1 grm. reduced Hb per cent. = 1·34 c.cm. O_2 unsaturation = 18·66 c.cm. O_2 content. A minimum of 5 grm. reduced Hb per cent. or 6·7 c.cm. O_2 unsaturation per cent. is the least amount which must be present in the capillary blood to produce cyanosis. An anæmic individual with less than 5 grm. Hb per cent. consequently cannot usually become cyanosed.

The cyanotic colour is due to the blood in the *minute vessels, i.e.* capillaries, and possibly in the arterioles and venules of the subpapillary plexus as well.

Factors Modifying Cyanosis.—1. Thickness of the epidermis, which itself has no vessels.

2. Presence of normal or pathological pigments in the skin.

3. Variations in the colour of the plasma from varying concentration of lipoids, white cells in leukæmia, pigments.

4. Variation in the concentration of oxyhæmoglobin in the blood.

5. Variation in the number, the width, and length of the blood-filled capillaries in a given area.

These modifying factors cannot alone produce cyanosis. They can influence the amount of reduced hæmoglobin (O_2 unsaturation) which is necessary to give the skin a perceptibly blue colour, and can modify the exact shade of colour produced. Factor 5 needs further consideration. With the skin microscope variations are noted in the denseness of the capillary network in different parts of the skin and at short intervals of time.[1] Great variations are present in the capillary distribution in different individuals. The influence of *temperature* is important. When the surrounding atmosphere becomes colder the arterioles are constricted and the capillaries dilated. The blood-flow becomes slow and extensive reduction of the blood may take place (cf. p. 297).

An *increased venous pressure* tends to increase the number, width, and length of the blood-filled capillaries, and the deeper vessels become

[1] The latter statement is denied by Lewis (p. 293).

visible; the production of cyanosis is thus facilitated. Increase in the *blood volume* may have a similar effect. These facts would help to explain the ready production of cyanosis in *polycythæmia*, in which there is an increased blood volume and possibly a hyperplastic condition of the capillaries as well.

To simplify subsequent considerations the following average standards are assumed (Lundsgaard and van Slyke):

Normal arterial blood=95 per cent. saturated with oxygen.
19 c.cm. O_2 content per cent.
1 c.cm. O_2 *unsaturation* per cent. (A).
O_2 utilization by tissues=5 c.cm. per cent.
Mixed venous blood=70 per cent. saturated with oxygen.
14 c.cm. O_2 content per cent.
6 c.cm. O_2 unsaturation per cent. (V).

Average unsaturation in the *capillary* blood is taken as the mean of the arterial and venous unsaturation=$\frac{A+V}{2}=\frac{1+6}{2}=3{\cdot}5$ c.cm. per cent. (*i.e.* 16·5 c.cm. O_2 content per cent.)

As already pointed out, the capillary unsaturation must rise to 6·7 c.cm. per cent. before cyanosis can develop.

Causes of Cyanosis.—It is obvious that the causes of anoxæmia and cyanosis must, to a large extent, overlap. The following classification (after Lundsgaard and van Slyke) may be used:

I. *All the blood passes through lung tissue accessible to air, but diffusion is hindered and oxygenation in the lungs is incomplete.*

This occurs in—

1. Low O_2 pressure in the alveoli (high altitudes).
2. Swelling and thickening of alveolar wall and consequently diminished permeability to oxygen ("pneumonosis").
3. Inefficient ventilation from shallow breathing.

If the arterial oxygen content falls as a result to *16 c.cm. per cent.*, cyanosis will be present.

$$A=4 \text{ c.cm.}; \quad V=9; \quad \frac{A+V}{2}=6{\cdot}5$$

which is the threshold for cyanosis.

II. *Presence of an unaerated shunt between the veins and arteries.*

(i) Congenital perforation of cardiac septum.

(ii) Collapse or consolidation of part of a lung with persistence of the blood-flow through the region. It can be calculated that if *over one-third* of the output of the heart is shunted from the right to the left side without being aerated, cyanosis develops.

Group I. are relieved by the administration of oxygen, which raises the oxygen pressure in the alveoli and increases the rate of diffusion into the blood. Group II. (i) is completely unaffected by oxygen therapy; (ii) can only be helped if the collapse is not quite complete, in which case oxygen inhalation may help to get some oxygen into the almost functionless areas.

III. *Greater reduction of oxyhæmoglobin in the tissues.*

(i) Local chilling of a part (within certain limits, p. 297), or rise of venous

pressure which retards the circulation, will slow down the local rate of blood flow and so increase the reduction of the blood.

(ii) Diminished circulation rate in heart failure is accompanied, as noted (p. 342), by high oxygen utilization in the tissues. Cyanosis may not be present at rest, but the increased oxygen consumption which accompanies activity may be adequate to raise the reduced hæmoglobin content to the required level.

The oxygen consumption of the tissues must rise to 12 c.cm. per cent. (normal=5 c.cm.), *i.e.* to two and half times the normal, before cyanosis can be produced by this factor alone.

Certain clinical conditions will be more fully considered.

(*a*) **Congenital Heart Disease.**—Cyanosis is only present in a proportion of cases (35 to 50 per cent.). Abnormal communication between the right and left side of the heart can occur if there is a patent septum or a patent ductus arteriosus. Unless other abnormalities are present as well, the blood must tend to flow from the left to the right side of the heart, owing to the higher pressure found on the left side. It has been shown, in support of this contention, that in uncomplicated cases of patent foramen ovale or large defects of the interventricular septum there is *dilatation* of the pulmonary artery and diminution in the size of the aorta, *i.e.* more blood than normal is passing through the pulmonary artery.

Pulmonary stenosis is often associated with congenital defects of the septa, and it is possible (though not proven) that this may form a sufficient obstacle to enable shunting to occur from the right to the left side of the heart. The right ventricular wall may then be as thick as the left, owing to hypertrophy of its muscle.

If any " shunting " is present, *exercise* may raise the resultant unsaturation to the cyanosis level by increasing the oxygen utilization in the capillaries. External *cold* would have a similar effect (p. 297).

Polycythæmia, *i.e.* an increase in the number of red cells per c.cm. to 7 or 8 million, is present as a rule (as a compensatory phenomenon), and this increases the viscosity of the blood. The flow through the capillaries is consequently slowed. The capillaries are said to be increased in width and number.

(*b*) **Mitral Lesions.**—There is increased pressure in the left auricle, which interferes with the pulmonary circulation, and therefore with the oxygenation of blood in the lungs.

(*c*) **Heart Failure.**—When heart failure develops from any cause, cyanosis is common. Œdema of the lung, hydrothorax, shallow breathing, all result in under-arterialization in the lungs. The diminished circulation rate produces capillary stagnation, high oxygen utilization and greater reduction of the blood, and therefore cyanosis.

(*d*) **Tracheal and Bronchial Stenosis.**—Cyanosis is common in marked tracheal obstruction, as a result of the decreased ventilation of the lungs. CO_2 retention adds to the distress experienced and the feeling of suffocation.

In bronchial stenosis cyanosis is uncommon. As, at least, one-third of the blood must pass through the unaerated channel, it follows that at least two-thirds of one lung must be shut off because of the bronchial obstruction before cyanosis appears.

(*e*) In *asthma* there is deficient pulmonary ventilation from bronchiolar

obstruction. In *bronchiolitis* there is patchy collapse of parts of the lung. The cyanosis of *emphysema* is often very marked. It is in part due to defective movements of the chest and inadequate pulmonary ventilation. Many of the pulmonary capillaries are obliterated and so there is incomplete oxygenation in the lungs (p. 371).

In lobar *pneumonia* and *œdema* of the lung there is arterial anoxæmia, for reasons sufficiently explained (pp. 340 and 339).

Acute *pneumothorax* is usually associated with cyanosis, because the blood-flow persists through the collapsed lung and perhaps because the displacement of the heart impedes its action. In cases of chronic pneumothorax, the collapsed lung tissue was previously not functioning normally, and its vessels were thrombosed. Cyanosis does not ensue, as no blood circulates through the collapsed lung.

(*f*) **Alteration in the Hæmoglobin of the Blood.**—We have noted that as a result of certain poisons, *e.g.* chlorates, methæmoglobin is formed, which gives the blood a dark colour (p. 341). Some of the coal tar preparations—acetanilide, sulphonal, trional—produce a similar result.

Sulph-Hæmoglobinæmia.—In this rare condition sulph-hæmoglobin is formed, giving rise to cyanosis of a leaden hue. The pigment is wholly intracorpuscular. Its mode of formation is not yet clearly understood. It must be remembered that sulph-hæmoglobin is not formed in blood when excess of H_2S is present in cases of poisoning with this substance. A strong reducing agent of unknown composition is present in the blood, urine, and saliva in sulph-hæmoglobinæmia. If the serum of these patients is added to whole blood, reduced hæmoglobin is soon formed. It has been shown (Clarke and Hurtley) that powerful reducing agents permit the formation of sulph-hæmoglobin from oxyhæmoglobin in the presence of minute traces of H_2S. It is suggested that the reducing agent found in the blood of these patients allows the normal traces of H_2S which are absorbed into the blood from the bowel to effect this conversion. A bacillus has been isolated from patients which bears some ill-understood relationship to the disease. It is readily recognizable, as it can disintegrate amino-acids to form nitrites ("nitroso bacillus") (Mackenzie Wallis).

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CARRIAGE OF CO_2 IN THE BLOOD

Data—Methods Dissociation curve of blood and bicarbonate solutions—CO_2 transport—Distribution between plasma and corpuscles—Caisson disease.

The following data about carbon dioxide in the blood must be remembered. They indicate the normal average findings in man. Variations above and below these figures are to be expected in healthy subjects.

Tension of CO_2: (i) in alveolar air, 40 mm. Hg; (ii) in arterial blood, 40 mm. Hg; (iii) in venous blood, 46 mm. Hg at rest, and higher during exertion (up to 60 mm. Hg).

Volumes of CO_2 per 100 c.cm. of blood: (i) arterial blood, 52 c.cm.;[1] (ii) venous blood at rest, 55 c.cm.; (iii) venous blood during exercise, up to 65 c.cm. or even more.

Methods.—If 100 c.cm. of plasma be exposed to the CO_2 pressure found in alveolar air (40 mm. Hg), only about 3 c.cm. of the gas will pass into solution. As arterial blood gives off about 52 c.cm. CO_2 per cent. when exposed to a vacuum, it follows that the difference between 52 c.cm. and 3 c.cm. must be present in blood in some kind of chemical combination. It is believed that the chemically bound CO_2 is carried in the form of *bicarbonate*. The term "bicarbonate" is deliberately employed to indicate that CO_2 is united with various bases, most of which, however, is Na as $NaHCO_3$.

If plasma be calcined and the ash analysed, it is found that more base is present (chiefly Na) than could be united with all the fixed acid radicles like Cl, PO_4, SO_4. It must be remembered that some of the PO_4 and SO_4 is formed during calcining by oxidation of the P and S present in the protein and in organic combination in the plasma. The discrepancy thus becomes still greater, suggesting that a considerable amount of base must have been combined with a *volatile* acid, *i.e.* carbonic acid. As there is always an excess of free H_2CO_3 in solution in the plasma, it follows that the compound cannot be a carbonate (*e.g.* Na_2CO_3) but must be a *bicarbonate* (*e.g.* $NaHCO_3$). If plasma is dialysed, it is found that the dialysate contains sodium bicarbonate in the concentration of 0·25 grm. per cent. (Bayliss), which is about the amount required.

We have then certain *a priori* grounds for suggesting that CO_2 is transported in the form of bicarbonate. To test this view we must compare the behaviour of whole blood and a simple solution of bicarbonate.

To obtain the *carbon dioxide dissociation curve* for blood, the same methods are employed as described in the case of oxygen. Fresh oxalated blood is brought into equilibrium with varying tensions of CO_2 in a tonometer. The CO_2 content of the sample is then determined by using Haldane's blood gas analysis apparatus. 1·5 c.cm. weak NH_3 solution and a pinch of saponin are added to the bottle, and 1 c.cm. of the blood is run in under cover of this alkaline fluid. The NH_3 combines with free CO_2 and prevents it being given off. The corpuscles are laked. The oxygen present in the blood is driven off in the ordinary way by means of potassium ferricyanide; 0·25 c.cm. of 20 per cent. solution of tartaric acid is put into the small tube; and the bottle is connected with the graduated burette. By spilling the acid into the bottle, the bicarbonate is decomposed.

The combined CO_2 is evolved and can be measured. If the total CO_2 content of the blood is required, an allowance must be made for the CO_2 which is left in solution in the bottle. [If blood is kept *in vitro* at 37° its bicarbonate content diminishes, owing to its being broken down by lactic acid which is formed from glucose (Evans).]

A curve can be plotted, the abscissa representing pressure of CO_2 and the ordinate volumes of CO_2 in c.cm. per cent. (see Fig. 96). It is noticed that as the CO_2 tension is increased, CO_2 is readily taken up; if the CO_2 tension

[1] The range of the normal is from about 45 to 56 c.cm. per 100 c.cm. blood.

is diminished, CO_2 is readily given off. In a vacuum, all the CO_2 which is present in the blood is given off readily and completely.

The behaviour of an artificial bicarbonate solution (*e.g.* 0·25 grm. per cent.) is quite different. Very little alteration in the CO_2 content is effected by varying the CO_2 tension ; when the CO_2 tension is raised more CO_2 passes into solution, and when the CO_2 tension is lowered some of the gas is evolved.

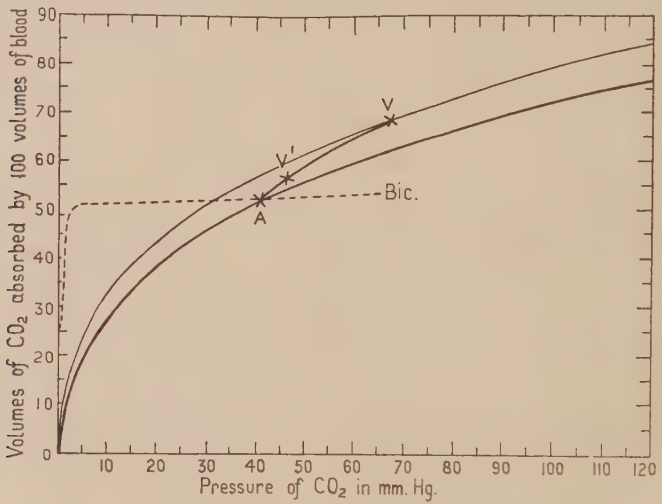


FIG. 96.—CO_2 Dissociation Curves of Blood.

Continuous lines : Lower curve : Dissociation curve of fully oxygenated blood ; Upper curve : Dissociation curve of blood, the hæmoglobin of which is fully reduced.—A = Arterial point ; V = State of blood which has been fully reduced in body and in which each 18·5 c.cm. O_2 used has given rise to an additional 15 c.cm. CO_2 (R.Q. = 0·8). AV = Dissociation curve of blood in body, when the increase of CO_2 content is accompanied by partial reduction of hæmoglobin. V' = State of mixed venous blood at rest in the body.

Dotted line (Bic.) = Dissociation curve of bicarbonate solution. Modified from CHRISTIANSEN, DOUGLAS and HALDANE.

In vacuo the bicarbonate dissociates very slowly, and only gives off *half* its CO_2 thus :

$$2NaHCO_3 \rightleftarrows Na_2CO_3 + CO_2 + H_2O.$$

One molecule of CO_2 still remains combined with base as Na_2CO_3, and it can only be displaced by means of acid.

To explain the peculiar properties of blood we must assume the presence of substances in plasma which can act on the bicarbonate and modify its behaviour. The addition of acid sodium phosphate to a bicarbonate solution enables it to give off CO_2 more easily ; but, as already noted (p. 223), the phosphate content (especially of the plasma) is very low. The serum proteins act in a similar way ; but plasma *in vacuo* does not give off all its CO_2 in a reasonable time ; about 5 per cent. of the CO_2 remains in the plasma, and can only be driven off by the addition of acid. If red corpuscles or hæmoglobin are added to plasma complete expulsion of CO_2 is speedily effected *in vacuo*.

The CO_2 dissociation curves of reduced and oxygenated blood can be

compared. In both cases the blood is exposed to an appropriate series of CO_2 tensions, but for the former the diluent gas in the tonometer is hydrogen, in the latter it is a mixture of hydrogen and oxygen, the latter being present in a sufficient concentration to exert 100 mm. pressure. Fig. 96 shows that at any given CO_2 pressure reduced blood is able to take up more CO_2 than oxygenated blood.

To understand the mode of action of hæmoglobin and the plasma proteins it must be remembered that blood is an alkaline fluid containing basic and acid radicles. The base is first seized and permanently bound with the strong acid radicles, *e.g.* Cl, to form salts like NaCl. The base which is left over is shared between the two weak acids, namely, H_2CO_3 and the proteins (which act as weak acids in an alkaline medium, p. 222), to form bicarbonate and proteinate respectively. Enough base is not available fully to neutralize these acids, and so we have left H_2CO_3, bicarbonate, " proteic acid " (protein acting as acid = HPr), and proteinate (protein combined with base = BPr.). A constant struggle goes on between the two acids for base and the amount they can obtain depends on their relative concentrations in the blood. If the H_2CO_3 of the blood is increased, base will be removed from the protein (using the term to include the protein of both plasma and corpuscles) and more bicarbonate is formed, and *vice versa*.

$$\underset{\substack{\text{(Protein}\\ \text{+base.)}}}{H_2CO_3 + BPr} \rightleftarrows \underset{\substack{\text{(Bicar-}\\ \text{bonate.)}}}{BHCO_3} + \underset{\substack{\text{(Protein}\\ \text{-base.)}}}{HPr}.$$

The equilibrium is thus a very unstable one, and is disturbed by variations in the mass of the interacting substances.

The protein chiefly under consideration is hæmoglobin, which is found in blood in both the reduced and the oxidized form. Oxyhæmoglobin is said to be about seventy times as strong an acid as the reduced form (Hill). Consequently oxygenation of the blood increases the mass action of the hæmoglobin and enables it to take base from bicarbonate and so turn CO_2 out of the blood ; conversely, reduction of the blood weakens the hæmoglobin as an acid, allows base to be yielded up to carbonic acid to form bicarbonate, and thus enable more CO_2 to be held in the blood at the given CO_2 pressure than otherwise would have been the case.

CO_2 Transport in the Body.—1. Arterial blood reaches the tissues with a CO_2 tension of 40 mm. Hg. As the CO_2 tension in the tissues is higher (perhaps 60 or 70 mm. Hg), CO_2 in solution diffuses rapidly into the blood and the CO_2 tension in the venous blood rises (at rest) to 46 mm. Hg. The amount of H_2CO_3 in solution is increased, and the equilibrium will be disturbed in its favour. Base passes from the hæmoglobin (directly and indirectly) and from the plasma protein and fresh bicarbonate is formed. Simultaneously, however, oxyhæmoglobin has yielded up some oxygen and has become partially reduced. It has thus become a weaker acid with a feebler hold on base. The H_2CO_3 is thus stronger and the proteins feebler in their capacity as acids. Base is therefore taken from proteins to form bicarbonate. The carbonic acid which obtains base and becomes transformed into bicarbonate is no longer present in the solution as CO_2, and thus room is made for more CO_2 to pass into the blood from the tissues. Venous blood at rest contains 55 c.cm. CO_2, and the amount which has been taken up is

3 c.cm. per cent. During exertion and tissue activity generally, the local CO_2 tension is higher, and the blood CO_2 tension is raised. Simultaneously the oxyhæmoglobin is more extensively reduced. Large amounts of base are transferred from the proteins, and a great increase in the bicarbonate formed occurs. The venous blood may contain 65 c.cm. CO_2 per cent. (chiefly in combination) under these conditions. The dilatation and increase in number of the capillaries help the taking up of CO_2 in the same way as they aid the giving off of oxygen.

Distribution of CO_2 between Plasma and Corpuscles.—We have suggested so far that base is obtained from the proteins of the blood to form bicarbonate in the tissues. This is true as a general statement, but additional details must now be given of the manner in which base is obtained for the carriage of CO_2 as bicarbonate.

(1). If blood is exposed to increasing tensions of CO_2, the chloride in the plasma diminishes, the bicarbonate of the plasma increases, and the chloride of the corpuscles increases (see p. 222).

i. $H_2CO_3+NaCl \gtrless NaHCO_3+HCl$ (in plasma).
ii. $HCl+KHb \gtrless KCl+HHb$ (in corpuscle).

The chloride shift or Hamburger phenomenon accounts for much of the necessary base. As explained on p. 222, although the base is primarily obtained from the NaCl of the plasma, reaction i. could not take place unless the HCl, which was formed, migrated into the red corpuscles and was buffered by the potassium hæmoglobinate present there.

(2). H_2CO_3 also diffuses into the corpuscles and obtains base directly from the hæmoglobinate.

iii. $H_2CO_3+KHb \gtrless KHCO_3+HHb$.

Potassium bicarbonate is thus formed.

According to van Slyke, 85 per cent. of the base necessary for the transport of CO_2 (*i.e.* for the formation of bicarbonate) is thus obtained directly (iii.) or indirectly (i. and ii.) from *hæmoglobin*.

(3). To a slight extent base is obtained from the plasma proteins and from the phosphate of the corpuscles.

iv. $H_2CO_3+NaPr \gtrless NaHCO_3+HPr$.
v. $H_2CO_3+Na_2HPO_4 \gtrless NaHCO_3+NaH_2PO_4$.

2. In the lungs, the venous blood (CO_2 tension at rest = 46 mm.) is exposed to an alveolar CO_2 pressure of 40 mm. Hg. Owing to the difference of pressure on the two sides of the membrane, CO_2 passes out of the blood into the lungs. As previously pointed out (p. 313) CO_2 diffuses very rapidly through the pulmonary epithelium, so that a pressure difference of 6 mm. is quite sufficient to enable the appropriate amounts of CO_2 to be evolved. The CO_2 pressure in the alveoli does not rise in spite of the addition of CO_2, which is turned out from the blood, because the breathing is regulated at a level which is sufficient to wash out as much CO_2 as is coming out from the blood. The CO_2 tension in the blood, when arterialized, falls to 40 mm. Hg, *i.e.* pressure equilibrium with the alveolar air is attained. The amount of H_2CO_3 in solution in the blood is therefore diminished and its mass action is reduced. The blood has meanwhile become oxygenated; oxyhæmoglobin has been formed, which is a stronger acid with a greater avidity for

base than reduced hæmoglobin. The equilibrium is thus disturbed in favour of the proteins of the blood. They take base from the bicarbonate and form more " proteinate " and hæmoglobinate. The CO_2 which has been deprived of its base cannot remain in the blood, which already holds as much CO_2 as it can in solution ; and consequently it must pass out into the lungs. Owing to the lower CO_2 tension in the alveoli and the action of the proteins as weak acids competing for base, about 3 c.cm. of CO_2 are given off in the lungs by 100 c.cm. of blood at rest.

A comparison of the upper (reduced blood) and lower (oxygenated blood) curves in Fig. 96 shows that in the physiologically important region (*i.e.* when the CO_2 tension is 40 to 50 mm. Hg), reduction of the blood enables it to take up five or six additional volumes per cent. of CO_2. Oxygenation of the blood helps to turn out CO_2[1] ; reduction of the hæmoglobin allows the venous blood to take up more CO_2. Equations i. to v. (*supra*) read from right to left illustrate in detail how the base is removed from the bicarbonate to liberate CO_2 (cf. p. 223).

If 100 c.cm. of blood are fully reduced in their passage through the tissues, 18·5 c.cm. O_2 are used ; if the respiratory quotient is the usual one of 0·8, 15 c.cm. CO_2 are formed. The CO_2 content of the blood would rise from 52 c.cm. (the amount of CO_2 which is present in 100 c.cm. of arterial blood), *i.e.* point A on the lower, *oxygenated* curve, to 67 c.cm. (V) on the upper curve of *reduced* blood. Reference to the curve shows that the CO_2 tension would then only be 62 mm. Hg. In the case of blood which remained fully oxygenated, an extra 15 c.cm. of CO_2 could only be taken up if the CO_2 tension rose to about 80 mm. Hg ; a great saving of CO_2 tension thus results from the fact that reduced hæmoglobin is a weaker acid than the oxygenated form. The line joining the points A and V represents the dissociation curve of CO_2 under the conditions which are present *in the body*. Allowance is made in this curve for the fact that the power of blood to hold CO_2 increases steadily as it becomes more reduced. Venous blood at rest contains about 55 volumes CO_2 per cent., and reference to the line AV shows that the necessary tension is only 45 or 46 mm. Hg.

As previously explained (p. 222) the reactions which have been discussed above not only show how CO_2 is transported from the tissues to the lungs and how it is expelled there, but also illustrate how the process is carried out with a minimum disturbance of the reaction of the blood. When CO_2 is taken up more H_2CO_3 is formed, and so the H ion concentration tends to rise ; but this is largely compensated for by the simultaneous reduction of the hæmoglobin (which thus becomes less acid) and by the formation of bicarbonate which gives rise to an excess of OH ions ; the reverse changes take place in the lungs. The bicarbonate of the plasma has three functions : (i) it acts as a means of *CO_2 transport* ; (ii) it is the *alkali* of the plasma (the reaction of plasma depends on the ratio of H_2CO_3 to $BHCO_3$) ; (iii) it is the *alkali reserve* which neutralizes any strong acids which enter the blood (p. 219).

REFERENCES

VAN SLYKE.—*Physiol. Rev.*, 1921, vol. i. p. 141.
HALDANE.—*Respiration*, New Haven, 1922.

[1] It is interesting to note that saturating the blood with carbon monoxide has the same effect.

Caisson Disease.—This is a condition which occurs in deep divers and in workers in caissons, *i.e.* steel chambers which are sunk in water and filled with compressed air. While the subject is in the caisson there is little discomfort except temporary giddiness and noises in the ears. The breathing and the pulse are slowed and there is frequency of micturition. Symptoms appear on coming out of the caisson, either immediately or after some hours.

1. Pain is felt in the joints or elsewhere in the body, which may force the subject to adopt an attitude of flexion (mild cases).

2. Paraplegia, *i.e.* paralysis of the legs.

3. Circulatory failure (cyanosis, imperceptible pulse) and death in a few minutes (severe cases).

Under high atmospheric pressures excess nitrogen is taken up in solution. On rapidly reducing the pressure, nitrogen is liberated in the form of bubbles which may block the circulation in any locality or accumulate in the heart and are frothed up with the blood. This prevents the emptying of the organ and so causes general circulatory failure. As nitrogen is five times as soluble in fat as in water, symptoms tend to be more severe in adipose subjects. The excess oxygen which is evolved is used by the tissues and causes no trouble.

The pressure in the caisson must be reduced in stages to enable the dissolved nitrogen to be gradually given off. If symptoms appear, recompression must be carried out at once.

MUSCULAR EXERCISE

Pulmonary ventilation—Oxygen intake—Circulation rate—Blood pressure—Supply of oxygen to tissues—Removal of oxygen by tissues—Muscular contraction—Lactic acid—Its formation, removal, and mode of action—Fatigue—Heat production—Mechanical efficiency—Varieties of exercise—Moderate exercise—Severe exercise—Respiratory quotient—Oxygen debt.

The first important problem in exercise is a respiratory one: How may the enormous demands of the active muscles for oxygen be met and, similarly, how may the CO_2 formed be eliminated? To illustrate the size of the burden which may be thrown on the body, it must be noted that the oxygen consumption may increase from 250 c.cm. per minute at rest to 4 or 6 litres per minute in strenuous exertion.

The reactions of the body may be summarized as follows:

1. *Increased pulmonary ventilation* is necessary to introduce large amounts of fresh air and oxygen into the lungs (and drive out CO_2). This is effected by stimulation of the respiratory centre—

i. By impulses from the higher centres even before the exercise begins.

ii. By the raised CO_2 tension in the blood (p. 320).

iii. In very strenuous exercise lactic acid may pass out from the muscles into the blood, break down the bicarbonate, and thus produce a definite rise in the H ion concentration (p. 321).

iv. Oxygen lack may possibly be a factor, as the blood is rushed so

rapidly through the lungs that perfectly complete oxygenation may not occur.

v. By the rise of body temperature (pp. 325, 378).

The most important factor is the chemical one—the rise of CO_2 tension and of H ion concentration. As the work becomes more severe, CO_2 is formed in greater amounts and the ventilation is increased in direct proportion. It may rise from a resting level of 5 to 8 litres per minute to 50 or even 100 litres per minute.

2. Large amounts of *oxygen* must be taken up from the lungs by the blood.

i. The mixed venous blood arrives at the lungs in a more reduced form. Instead of the venous oxygen content being 15 c.cm. and the amount of oxygen taken up from the alveolar air being 3·5 c.cm. per cent., the venous blood may contain 7 c.cm. during hard work or even as little as 3·5 c.cm. during very strenuous exertion, and therefore take up 11·5 or 15 c.cm. per cent.; *i.e.* the oxygen intake is by this mechanism alone increased up to fourfold.

ii. A greatly increased venous return (see pp. 263, 264) enables the heart to pump more blood per minute through the lungs. This is brought about in two ways:

(*a*) Increase of the stroke-volume, *i.e.* the output per beat, which may rise to 200 c.cm. (p. 264).

(*b*) Acceleration of the heart up to 150 or over per minute. This is due to—

α. Impulses from the higher centres.

β. Auricular reflex, set up as a result of the raised venous pressure in the right auricle (p. 258); this is probably the principal factor concerned and increases the heart rate in proportion to the rise in venous return.

γ. Rise of CO_2 tension and O_2 lack acting on the cardiac centre (p. 259).

δ. Rise of temperature (pp. 242, 259).

The circulation rate may reach 30 or even 40 litres per minute, *i.e.* it too is increased fourfold. As each unit of blood may take up four times the amount of oxygen which it does at rest, the oxygen intake may be raised sixteenfold.

3. *Supply of Oxygen to the Tissues.*—i. The output of the left heart is increased to exactly the same extent as the right heart, *i.e.* up to 30 or 40 litres per minute.

ii. The blood is *redistributed* so that a greater proportion of it is sent to the active regions. In exercise the muscles may receive a blood-flow perhaps eighteen times as great as normal. This is achieved by constricting the vessels of the splanchnic area and the skin, and driving the blood under increased pressure to the muscles. The coronary and cerebral vessels benefit too, because the rate of flow through these structures is speeded up. The redistribution of the blood is effected as follows:

The vasomotor centre is stimulated by (α) impulses from the higher centres, (β) perhaps reflexly from the active muscles, (γ) increased CO_2 tension, rise of H ion concentration, and O_2 lack (p. 292).

Adrenaline is probably secreted in these states of stress, and aids in the redistribution of blood by constricting arterioles which receive a marked vasomotor innervation; it dilates the coronary arteries and increases the

blood supply to the heart; it also contracts the spleen and raises the oxygen-carrying power of the blood (p. 132).

The *blood pressure* rises, *e.g.* to 160 or 180 mm. Hg. As the output of the heart increases threefold or more, one would have expected the blood pressure to rise in the same proportion. The fact that the rise of blood pressure which is observed is relatively small shows that, on the whole, the *peripheral resistance in exercise is decreased, i.e.* the dilatation of the vessels which supply the muscles outweighs the constriction in the splanchnic area and skin which is brought about by adrenaline and by impulses from the vasomotor centre.

4. *Removal of Oxygen by the Tissues.*—i. Dilatation and increase in the number of the capillaries in the muscles (p. 292), which slows the rate of the blood-flow and allows more time for gaseous exchanges.

ii. Low oxygen tension in the tissues, which allows oxygen to diffuse more readily and to a greater extent out of the blood.

iii. High CO_2 tension and raised temperature increase the extent and rate of dissociation of oxyhæmoglobin (p. 334).

The blood which leaves the tissues is thus very extensively reduced, and the mixed venous blood may contain as little as 3·5 c.cm. oxygen instead of the usual 15 c.cm. per cent. As stated, it has been shown experimentally, the coefficient of oxidation of muscle may rise from 0·003 c.cm. at rest to 0·08 c.cm. per grm. per minute during activity, an increase of thirtyfold. This is achieved by increased blood-flow (*e.g.* $\times 10$) and increased utilization of oxygen (*e.g.* $\times 3$).

It will be noticed how every part of the body makes its contribution to the general effort. The pulmonary bellows supply the oxygen. The heart and vasomotor mechanism send the blood mainly to parts which need it. The tissues abstract as much oxygen as they can from the blood supplied to them. The elimination of CO_2 is brought about in the same way.

The respiratory and circulatory changes persist *after* the exercise is over to an extent which depends on the severity of the exertion (p. 359, *et seq.*).

Muscular Contraction.—Freshly excised resting muscle has a negligible lactic acid content. If the muscle is stimulated in the absence of oxygen (*e.g.* in an atmosphere of nitrogen), it can respond normally (*i.e.* contract and relax) for some time, and lactic acid accumulates in the muscle. The appearance of lactic acid coincides with a quantitative disappearance of muscle glycogen. When the lactic acid concentration reaches 0·24 to 0·4 per cent. the muscle usually fails to respond to stimuli. This level is called the "*lactic acid maximum.*" If *resting* muscle is kept in nitrogen (condition of "anaerobiosis") slow spontaneous lactic acid formation takes place, and this too is accompanied by equivalent disappearance of glycogen. If fatigued muscle is still kept in an oxygen-free atmosphere, further accumulation of lactic acid occurs. When it reaches 0·5 to 0·65 per cent. it causes the muscle proteins to coagulate, and the condition called *rigor mortis* results.

The following scheme represents the events which are believed to precede the formation of lactic acid. The process is *anaerobic*, for, as already stated, it can occur in the complete absence of oxygen. There are probably many intermediate products in the disintegration process, the most important of which is methyl glyoxal (or pyruvic aldehyde, $CH_3CO.CHO$) which can be

found *in vitro* in the alkaline hydrolysis of glucose. It is readily transformed into lactic acid, $CH_3CHOH.COOH$.

Glycogen
$(C_6H_{10}O_5)_n$
↓
2 Methyl glyoxal
$(CH_3CO.CHO)$
↓
2 Lactic acid
$(CH_3CHOH.COOH)$

Fatigue in isolated muscle is not due to exhaustion of the available stores of glycogen, for the lactic acid maximum is usually attained before all the muscle glycogen is used up. The rise of H ion concentration plays an important part: thus the lactic acid maximum in *minced* muscle (in which glycogen breakdown occurs in the same way as it does in contracting muscle) kept in a slightly *acid* solution (pH = 4·5) is under 0·1 per cent. On the other hand, a higher lactic acid maximum than usual is obtained with muscle placed in an *alkaline* solution, particularly if alkaline *sodium phosphate* is used, when lactic acid concentrations as high as 0·8 per cent. have been recorded. The last fact mentioned suggests that phosphate plays a special rôle in muscular contraction. Other observations pointing in the same direction are as follows: muscle extracts incubated with glucose *in vitro* cannot form lactic acid, but will do so if phosphate is also added; they can break down hexose phosphate to form lactic acid. It has been suggested that hexose phosphate is an intermediate stage in the conversion of glycogen to lactic acid, and this substance has therefore been called "lactacidogen" (Embden, cf. p. 356). Increased excretion of phosphate in the urine takes place after exercise; it is also claimed that the maximum possible effort of trained men is increased by the ingestion of phosphate.

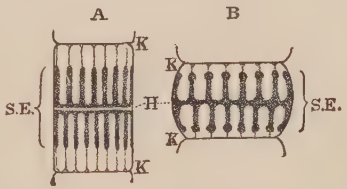


Fig. 97.—Diagram of Structure of Sarcomere.—Sharpey-Schafer.

S.E. = Sarcous element (dark part of sarcomere, "spongioplasm"); H = Hensen's line; K = Krause's membrane; A = Moderately extended condition; B = Contracted condition.

It has recently been shown that phosphate is present in muscle combined with *creatine* to form a substance called *phosphagen*.[1] If isolated muscle is kept under *anaerobic* conditions the phosphagen steadily breaks down, and coincident with this process there is equivalent formation of creatine and a rise in the inorganic phosphate content of the muscle. The phosphagen breakdown does *not* run parallel with the production of lactic acid; the phosphagen has almost completely disappeared before the lactic acid has reached a quarter of its final value. Phosphagen is resynthesized when fatigued muscle is exposed to oxygen, and this process proceeds more rapidly

[1] Eggleton, *Biochem. Journ.*, 1927, vol. xxi. p. 190; *Journ. Physiol.*, 1928, vol. lxv. p. 15. Fiske and Subbarow, *Science*, 1927, vol. lxv. p. 401.

than the restitution of lactic acid to form glycogen (*v. inf.*). Phosphagen is also destroyed as a result of activity ; part of the P appears as inorganic phosphate and the rest as an acid-soluble organic ester of phosphoric acid which is said to be identical with the " lactacidogen " of Embden. It will be noticed that according to Embden " lactacidogen " is *broken down* during the muscular contraction, while according to Eggleton " lactacidogen " is *synthesized* as a result of contraction.

Mode of Action of Lactic Acid.—The fibres of skeletal muscle consist of a series of striated fibrils or sarcostyles between which is found undifferentiated sarcoplasm. The fibrils show alternating light and dark bands. The former are divided by Krause's membrane, the latter by Hensen's line. A sarcomere is that portion of a fibril which lies between two membranes of Krause. The functional unit of muscle from the histological standpoint is half a sarcomere, Hensen's line dividing the latter into two independent entities. During contraction, it is thought that the clear material (" hyaloplasm ") flows into the darker " spongioplasm." There is no satisfactory explanation as yet of the mechanism of the muscular contraction ; the appearance of lactic acid in the muscle and the consequent liberation of H ions is associated with contraction ; when lactic acid is neutralized and the H ions are removed, *relaxation* occurs ; but whether lactic acid is actually responsible for the contraction, and, if so, how it acts, is as yet unknown. The neutralization is probably effected by the muscle proteins thus :

$$\underset{\text{(Lactic acid)}}{HL} + NaPr \gtrless \underset{\text{(Sodium lactate)}}{NaL} + HPr \quad \text{(Meyerhof.)}$$

As lactic acid accumulates the muscular contraction becomes smaller and more gradual ; relaxation also takes place more slowly and incompletely. Finally, when excessive amounts of lactic acid are present they alter the state of the muscle colloids in such a manner that further contraction becomes impossible, *i.e.* complete *fatigue* is present. The *p*H of resting muscle is 7·2 ; in complete fatigue it is about 6·7 ; in rigor mortis it is not more than 6·3. These relatively small changes of H ion concentration in the presence of large amounts of lactic acid show how efficient is the buffering action of the muscle proteins.

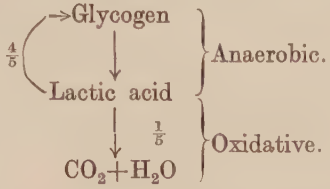
Removal of Lactic Acid.—If a fatigued muscle is placed in oxygen it recovers slowly : the accumulated lactic acid disappears and excitability returns. In the case of *injured* muscle, lactic acid is formed, which does *not* disappear in the presence of oxygen. The removal of lactic acid is therefore an *oxidative* process, *i.e.* it needs the presence of oxygen, and it depends to some extent on the intervention of living tissue. The lactic acid is disposed of as follows :

1. About one-fifth of the lactic acid which disappears is oxidized to CO_2 and H_2O, as can be calculated from the oxygen consumption and the CO_2 output of the muscle during the recovery process ; and the respiratory quotient is exactly 1.

$$CH_3CHOH.COOH + 3O_2 \longrightarrow 3CO_2 + 3H_2O.$$

2. The remaining four-fifths of lactic acid are reconverted into glycogen, which reappears in the muscle in the appropriate amount.

This latter process is anaerobic, like the breakdown of glycogen to lactic acid :



Heat Production.—If a muscle is stimulated to contract *isometrically*—*i.e.* by pulling against a spring which it cannot overcome—the length of the fibres remains unaltered, but the tension in the muscle increases. All the energy of the chemical changes is converted into heat, which can be measured by means of a sensitive thermopile.

1. If a muscle is stimulated to contract isometrically in the *absence* of oxygen (*anaerobically*) heat is evolved. The amount of heat produced when 1 grm. of lactic acid is liberated in living muscle is 385 (small) calories.[1] Practically the whole of this heat is "*initial*" heat, *i.e.* it is evolved during the process of contraction and relaxation ; about 11 per cent., however, is evolved not initially, but during the 15 minutes following stimulation, from sources which have not yet been definitely ascertained. The amount of heat which is associated then with the formation of lactic acid is 89 per cent. of 385 = 344 calories. The heat of combustion of 1 grm. glycogen dissolved in water is 3836 calories ; that of lactic acid is 3601 calories. The formation of dissolved lactic acid from dissolved glycogen yields therefore 235 calories. This leaves 344—235 = 109 calories still unaccounted for. The heat of neutralization of 1 grm. lactic acid by a buffered protein mixture is 122 to 138 calories (Meyerhof) ; that by an alkaline salt is 19 calories. If we suppose that most of the lactic acid is buffered by the muscle proteins and a small amount by $NaHCO_3$ or Na_2HPO_4 , the rest of the initial heat is satisfactorily accounted for. The amount of initial heat formed is the same under aerobic as under anaerobic conditions ; it can be attributed to the two known chemical reactions which accompany contraction and relaxation, *i.e.* the formation of lactic from glycogen and its subsequent neutralization (Hill).

2. In the presence of *oxygen* (*aerobically*), the lactic acid (strictly speaking, lactate) which has been formed is removed. This process is accompanied by further liberation of heat —"*delayed*" *heat*, so called because it is given off after the muscle twitch is completed. Most of the delayed heat is evolved during 20 to 30 seconds following muscular activity, but it goes on in steadily diminishing amount for about 5 minutes. The delayed heat is 1·5 times the initial heat. About one-fifth of the lactic acid present is disposed of by oxidation ; this is an *exothermic* reaction which gives off heat. The other four-fifths (approximately) of the lactic acid is reconverted back into glycogen ; this is an *endothermic* reaction, *i.e.* one which requires heat to enable it to take place. Some of the energy liberated from the combustion of lactic acid is used in the reconversion of the major portion of the lactic acid to glycogen ; the rest of the energy of the combustion is liberated as the

[1] All the calories referred to in this section are *small* calories.

delayed heat. As the lactate is removed, the sodium which was united with it recombines with the muscle proteins

The thermal changes may be summarized thus : (Hill)

		Small Calories per 1 grm. Lactic Acid formed.
(i) Initial heat,	1·0	344
(ii) Anaerobic delayed heat	0·12	41
(iii) Aerobic delayed heat	1·5	516
(iv) Total anaerobic heat (i + ii)	1·12	385
(v) Total aerobic heat (i + iii)	2·5	860

860 small calories are therefore evolved in muscle when 1 grm. lactic acid is formed from glycogen, neutralized, and disposed of. If the whole of the lactic acid were oxidized, the heat evolved would be 3836 calories, *i.e.* the heat of combustion of 1 grm. glycogen. Therefore $\frac{860}{3836} = 0{\cdot}224$ grm. glycogen are oxidized in one complete cycle in which 1 grm. of lactic acid was produced.

Work of Muscle.—When a muscle contracts *isotonically*, *i.e.* when it is permitted to shorten and move a weight, work is done. The ratio $\frac{\text{energy converted into work}}{\text{total energy liberated}}$ = mechanical efficiency. In the case of isolated muscle under optimum conditions about 40 per cent. of the total energy of the chemical changes which occur during the cycle described above is converted into work.

In the human subject lower figures are obtained : in an athlete the mechanical efficiency is about 25 to 30 per cent.. in an untrained person 20 to 23 per cent. With each kind of work there is an optimum *rate* of contraction at which the movement is carried out with a maximum efficiency.

Fenn has recently made the remarkable discovery that when a muscle is allowed to shorten (contract isotonically) more energy is made available than when it is contracting isometrically ; some source of energy seems to be called upon which was not utilized (or not fully utilized) under isometric conditions. The excess energy liberated is proportional to the work done. These points are brought out in the following table (after Fenn) :

Contraction.	Weight Lifted.	Work Done.[1]	Heat Liberated.[1]
Isometric . .	∞	0	7·3
Isotonic . . .	50 grms.	1·26	9·3
,, . . .	100 ,,	1·88	10·5
,, . . .	200 ,,	1·90	11·5
Isotonic . . .	300 grms.	0·62	8·6

The greater the *initial length* of skeletal muscle fibres the greater is the energy liberated during isometric contraction and the greater the amount of

[1] Expressed in ergs × 10^4.

work realized during isotonic contraction ; beyond a certain point, however, further extension of the fibres diminishes the energy of the contraction (cf. p. 240). The absolute refractory period of the frog's sartorius is about 0·003 secs., excitability returns in 0·02 sec. and may then pass through a supranormal phase (cf. p. 13, and p. 240). Rise of temperature increases the *rate* at which development of tension takes place, but reduces the tension set up on contraction. The rate at which lactic acid is removed in oxygen (i) increases with rise of temperature ; (ii) varies as the *square* of the concentration of lactic acid which is present ; (iii) depends on the *p*H of the fluid in which the muscle is immersed : on the *acid* side of neutrality any rise of H ion concentration of the surrounding fluid retards the speed of the recovery process, but on the alkaline side of neutrality the rate is independent of change of *p*H.

"Excess Metabolism" of Exercise.—The resting oxygen consumption and CO_2 output are first determined by means of the Douglas bag technique. The expired air is then collected *during* and *after* exercise, and the gaseous exchanges again determined. The metabolism over and above the resting level can thus be measured, and is termed the "*excess metabolism of exercise.*"

	Resting.	During Exercise.	Excess.
O_2 consumption. .	250 c.cm. per min.	1250 c.cm.	1000 c.cm.
CO_2 output. . .	200 c.cm. „	1200 c.cm.	1000 c.cm.

The ratio between the excess CO_2 output and the excess O_2 consumption is called the *respiratory quotient of excess metabolism.*

Varieties of Exercise.—Two main types of exercise can be recognized —*moderate,* which can be continued for long periods, and *very strenuous exercise,* which can only be kept up for a short time.

1. **Moderate Exercise.**—The R.Q. of excess metabolism is found to be *unity.* All the energy of the muscular contraction must therefore be derived from carbohydrate. One-fifth of the lactate which is formed is burnt with an R.Q. of 1 ; the other four-fifths are reconverted into glycogen by an endothermic reaction which involves no gaseous interchanges. In this type of exercise, the various reactions discussed on p. 352 are brought into action. Large amounts of oxygen are taken up in the lungs owing to the high circulation rate and the reduced state of the venous blood. The output of the left heart is largely diverted to the active muscles, the arterioles of which are relaxed to receive the increased blood-flow. The capillary changes and the oxygen "vacuum" in the tissues result in a high coefficient of utilization, and thus very large amounts of oxygen are supplied to the muscles.

Blood Reaction.—The lactic acid is dealt with almost as rapidly as it is formed ; it is completely buffered by the muscle proteins and then disposed of by oxidation and reconversion into glycogen. Very little lactic acid escapes into the blood stream. The H ion concentration of the blood only rises slightly from accumulation of H_2CO_3 and so there is no marked respiratory distress. To carry out this type of activity a liberal blood supply and efficient oxygen utilization by the muscles are essential.

The rate of oxidative removal of lactic acid will vary directly with the square of the lactic acid concentration in the muscles. If the exercise is kept up at a constant speed, the lactic acid in the muscle rises slowly from the resting minimum value to a certain level at which the rate of formation and removal are equal. The concentration of the acid in the muscle then remains stationary. Similarly, the oxygen consumption of the muscles (and of the body) rises continuously to a steady level which is maintained throughout the exertion, and then falls after the exercise is over.

Circulation Rate.—In running at the rate of 9 miles per hour an oxygen intake of about 4 litres per minute is attained, and can be kept up for half an hour. This involves a circulation rate of 30 litres per minute as explained on p. 261, which is the highest obtained in the human subject when breathing air. If oxygen is breathed during the period of exercise, the oxygen consumption may be as high as 5·9 litres per minute, and the circulation rate therefore is over 40 litres per minute. This latter figure probably represents the limits of bodily reaction.

After steady exertion in a trained subject, the breathing returns practically to normal within 6 to 8 minutes of terminating the exercise. This is the time necessary for completing the process of oxidative removal of lactic acid in the muscles and of any small amounts that have escaped into the blood stream.

Fatigue.—In steady, prolonged exercise this is probably due to a number of factors. Owing to the high circulation rate which may be necessary, the venous blood is rushed very rapidly through the lungs and may therefore be imperfectly oxygenated. We have already noted that a slight fall in oxygen tension of the arterial blood adversely affects the higher centres and induces a sense of fatigue ; a slightly diminished oxygen supply to the heart may impair its efficiency and decrease its output, so that the circulation may become inadequate for the needs of the body. The slight rise of H ion concentration may depress the brain. Lastly, discomfort is set up in the muscles from the local changes that develop there, and afferent impulses from these regions contribute to the sense of weariness.

2. **Severe Exercise.**—*Pulmonary Ventilation.*—In this type of exercise which is necessarily of relatively brief duration, the breathing remains much above the resting level for a prolonged period after the exertion is over. In the case of a man who ran 225 yards in 23·4 seconds, the pulmonary ventilation returned to normal in 27 minutes ; after a quarter-mile race followed by severe gymnastics, in 44 minutes ; after "standing running" for 4 minutes (breathing oxygen), in 87 minutes.[1] In the case of a 100 yards sprint, the subject may scarcely draw breath during the race, but marked dyspnœa develops later.

Lactic Acid formation.—During very violent exercise lactic acid is formed in amounts far greater than can be disposed of contemporaneously by the muscles. During hard running lactic acid may be liberated at the rate of *3 or 4 grms. per second.*

Three molecules of oxygen are necessary to burn one molecule of lactic acid, $C_3H_6O_3 + 3O_2 \rightarrow 3CO_2 + 3H_2O$. As stated, about four molecules of lactic acid are reconverted to glycogen for each molecule which is oxidized. There-

[1] These examples are quoted again on p. 363, in which the oxygen debt incurred and the lactic acid accumulated are discussed.

fore if *three* molecules of oxygen are used, *five* molecules of lactic acid must have been removed.

$$\therefore \text{ 1 grm. molecule } O_2 \text{ used means } \frac{5}{3} \text{ molecules HL removed.}$$

1 grm. molecule O_2 occupies 22·4 litres; the molecular weight of lactic acid is 90.

$$\therefore \text{ 22·4 litres } O_2 \text{ used means } 90 \times \frac{5}{3} = 150 \text{ grms. HL removed.}$$

∴ each 1 litre of oxygen which is used results in the removal of about 7 grms.[1] lactic acid.

Blood Lactic Acid.—The maximum oxygen intake per minute breathing air is about 4 litres, equivalent to 28 grms. lactic acid. As lactic acid is being formed at a much greater rate than this, it first accumulates in the muscles. Lactic acid is a freely diffusible substance which can pass freely from the muscles into the plasma, and *vice versa*; it therefore passes out into the blood stream. The resting level of lactate in the blood is of the order of 10 to 20 mgrms. per 100 c.cm. As a result of violent exercise the concentration of lactate may rise to 100 or, in exceptional cases, even to 200 mgrms. per 100 c.cm. (after 9½ minutes' strenuous exercise breathing oxygen). The highest level is usually attained *after* cessation of the exercise, because of the lag between muscles and blood. Following on this the blood lactate concentration steadily diminishes and reaches normal after a variable period of time up to 60 minutes or longer.

Respiratory Quotient.—The respiratory quotient of excess metabolism is determined during and after the period of exertion. It is found to rise at first above 1 and may reach 1·5 or 2; the highest figure recorded is 2·6. The maximum figure is usually attained shortly after the end of exercise. The R.Q. then falls below normal, *e.g.* to 0·5 or even as low as 0·2. These changes can be readily accounted for. The lactic acid which, as we have just noted, escapes into the plasma is buffered as usual by the bicarbonate.

$$HL + NaHCO_3 \rightleftarrows NaL + H_2CO_3.$$

This reaction results in the liberation of large amounts of CO_2, without any equivalent utilization of oxygen. In addition, lactic acid is disposed of in the muscle in the usual way, oxygen being used and CO_2 evolved with an R.Q. of 1. When the R.Q. of excess metabolism is 2·6, for each 1 molecule of CO_2 resulting from the oxidation of lactic acid in the muscles, 1·6 molecules of CO_2 are evolved from the $NaHCO_3$ of the plasma. The extent to which the R.Q. exceeds 1 is a good index of the intensity of the exertion.

Oxygen Debt.—After the exercise is over there is a final outpouring of lactic acid into the blood and the R.Q. reaches its highest level. The sodium lactate which is formed in the plasma ionizes into Na^+ and lactate$^-$. The oxygen consumption does not immediately fall to normal, but remains for a considerable time above the resting level until recovery is complete. The amount of oxygen which is used after cessation of the exercise in excess of the resting oxgyen utilization for the same length of time is called the *oxygen debt* (p. 362). This oxygen is first used to dispose of the lactate accumulation in the muscles. The lactate ions in the plasma diffuse back

[1] Recent work of Hill suggests that 1 litre of oxygen is equivalent to 6 grms. of lactic acid; the calculations on p. 363 would have to be modified accordingly.

slowly into the muscles as the lactate concentration diminishes there owing to the process of oxidative recovery. They are oxidized there in the ordinary way, oxygen is used, and CO_2 is formed with an R.Q. of 1 (the molecules of lactic acid which are converted into glycogen do not affect the respiratory exchanges because the process is anaerobic). But the CO_2 thus formed is *retained in the blood* to a considerable extent instead of being blown off in the lungs. It unites with the Na^+ of the plasma which was previously combined with lactate (as sodium lactate) to *re-form* the bicarbonate which has been depleted during the period of exercise; the low R.Q. which follows violent exercise is thus explained.

Blood Reaction.—As stated, in severe exertion lactic acid passes into the blood; there is an increase in the CO_2 and a fall in the bicarbonate content of the plasma. These two factors produce a demonstrable increase in the H ion concentration. This *acidæmia* stimulates the respiratory centre and increases the pulmonary ventilation to an extent which is sufficient to give rise to subjective symptoms of distress or *dyspnœa*.[1] The acidæmia is still present, of course, at the end of this severe type of exercise. The ventilation, therefore, does not return to normal for a prolonged period, *e.g.* half an hour after the exercise is over, or not for 80 minutes; as already pointed out, throughout this time the oxygen consumption remains above the resting level.

It is clear from this discussion that strenuous exercise does *not* depend on *concurrent* oxidation; lactic acid is formed in amounts far greater than the maximum oxygen intake can cope with. As we saw in the case of the isolated muscle, contraction can go on even when lactic acid is accumulating, and in this type of exertion lactic acid is piling up in the muscles. The excess lactic acid in man is temporarily buffered in the tissues and in the blood stream, and is disposed of *after* the exercise is over. We are thus permitted to do work far in excess of the greatest oxygen supplies which the heart and lungs can provide at the time, and we accumulate lactic acid. We overdraw our oxygen account during the exercise and repay the debt later. The size of the repayment is, of course, equal to the oxygen debt incurred during activity. The acidæmia which is still present at the end of exercise serves as a guarantee that the ventilation will be adequate to supply all the oxygen necessary for the recovery process. The excess oxygen consumption is at first high, during which period the lactate which is present in the muscles is dealt with. Then there is a prolonged phase during which lactate, which has overflown into the plasma, diffuses back slowly into the "oxidative machine" in the muscles, where alone it can be burnt. Very little lactate is excreted in the urine, and the amount thus eliminated is no index of the amount of lactic acid formed.

The amount of lactic acid which is present in the body at the end of a period of violent exercise can be calculated from the oxygen debt (1 litre O_2 is equivalent to 7 grms. lactic acid (p. 361)). In this way the results given in table on p. 363 have been obtained.

Fatigue.—We may assume that the muscles form 40 per cent. of the weight of the body. Only three-fourths of the muscle bulk is used during exercise, *i.e.* 30 per cent. of the body weight. The lactic acid accumulated in the body at the end of exercise in the above experiments is about 0·8 grm., 1·3 grm., and 1·8 grm. per kgrm. of body weight. If all this lactic acid were present in the muscles, the local concentrations would be 0·25, 0·45, and 0·6 per cent.

[1] See p. 368.

	O_2 Debt.	HL Accumulation.
i. Running 225 yds. on the flat in 23·4 secs. . .	8 litres.	56 grms.
ii. Quarter-mile race, followed by violent gymnastics for 30 secs., leading to complete exhaustion.	13 litres.	91 grms.
iii. "Standing-running," all out for 3½ min., breathing 50 per cent. oxygen	15–18 litres.	105–126 grms.

(Hill.)

If we assume that one-third of the lactic acid has escaped into the blood, the concentrations in the muscles are still 0·16, 0·3, and 0·4 per cent. As stated (p. 354), the fatigue maximum in isolated muscle is about 0·35 per cent.; if the muscle is kept in Ringer's solution to which alkali has been added, the maximum lactic acid concentration that can be attained is 0·5 per cent. or over. These experimental figures agree well with those obtained in exercise and suggest that the utter exhaustion of an athlete at the end of violent exercise is not due to fatigue of nervous elements, but to the lactic acid maximum having been reached in the muscles so that they can no longer contract. We can therefore say that the ability to carry out sudden violent exercise depends first on buffering of lactic acid in the muscles and then on the oxygen debt.

Training may increase the local buffering power of the muscle proteins by increasing the salts of the weaker proteins which yield base more readily. As these are used up, the less suitable proteins must be called upon, and a rise of cH occurs in the muscle. This results in a semi-permanent physico-chemical change in the colloidal structure of the tissue leading to loss of power, pain, and stiffness. As suggested (p. 304), some of the stiffness may be due to swelling of the muscle from accumulation of exuded fluid from the blood.

On a *fat* diet the R.Q. of the total excess metabolism of exercise, if the exercise is brief, is 1 (as in the normal person). If the exercise is prolonged, the R.Q. falls below 1 down to 0·7, indicating that fat is being used as fuel. As there is no evidence that fat can be utilized directly by muscle (p. 430) it is probable that it is first transformed into carbohydrate (possibly in the liver) and then sent to the muscles to serve as the source of energy.

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TISSUE OXIDATION

Superoxides and peroxidase—Glutathione—Rôle and mode of action—Hydrogen transport—Iron—Salvarsan—Nucleus and cell structure.

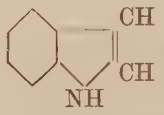
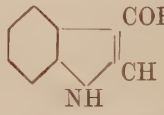
We have seen how the blood supply to the tissues is regulated in accordance with their needs, how oxygen is abstracted from the blood, and how the

tissues are sometimes allowed to carry out activities for which oxygen is supplied later. We now have to consider how the processes of oxidation are carried out within the cells.

The end products of digestion (*e.g.* glucose) are *dysoxidizable* substances, *i.e.* they do not readily unite with molecular oxygen at body temperature. Oxidation must be facilitated by the presence of catalytic agents.

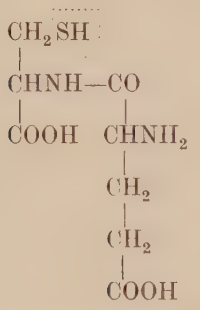
1. It seems probable that substances are present in small but adequate concentration in the tissues which combine with oxygen to form "*superoxides*" (analogous with hydrogen peroxide), which possess powerful oxidizing properties.

Many of the oxidative processes which occur in the body can be carried out *in vitro* by H_2O_2 alone of all the oxidizing agents known to us, *e.g.* oxidation of butyric acid ($CH_3CH_2CH_2COOH$) in the β position to β-oxy butyric acid ($CH_3CHOHCH_2COOH$);

of indol  to indoxyl  ;

of glycerol $CH_2OHCHOHCH_2OH$ to glyceric aldehyde $CH_2OHCHOHCHO$, and many others (Dakin). This strongly suggests that superoxides are present in the body. H_2O_2 itself cannot play this rôle in the tissues because of the widely distributed *catalase* which destroys it to H_2O and O_2. Just as outside the body the action of H_2O_2 is facilitated by catalytic agents like manganese, so substances may be present in the tissues—ferments called *peroxidases*—which aid the action of the superoxides.

2. **Glutathione.**—Hopkins has isolated a substance called *glutathione* from tissues, and he regards it as being one of the main factors in tissue oxidation, by acting as a hydrogen acceptor; recently this compound has been *synthesized* and its chemical identity definitely established. Glutathione exists in a *reduced* and in an *oxidized* form. The reduced form consists of glutamic acid combined with *cysteine*, the oxidized form of glutamic acid united with *cystine*. The formula of the reduced form is



Notice that the amino-grouping of the cysteine is united with one of the carboxyl groups of glutamic acid. The part of the molecule which is not enclosed by the dotted lines is, for the sake of simplicity, written as G.; reduced glutathione can be written as G.SH. The oxidized form of glutathione may be represented as G.S—S.G.

It must be remembered that by oxidation is meant addition of oxygen or *removal of hydrogen*.

Free cystine is not present in the tissues, so it is probable that most of the sulphur in cells is in the form of glutathione. The percentage concentration of this substance in liver is 0·18 to 0·24, in skeletal muscle 0·034 to 0·045, and in yeast 0·18.

The glutathione of the tissues is present in the *reduced* form ; it can be demonstated qualitatively by means of the *nitroprusside test.* To the tissue extract add a few c.cm. of saturated ammonium sulphate, 2 or 3 c.cm. of a solution of sodium nitroprusside and then excess of NH_4OH ; an intense purple (permanganate) colour develops if glutathione is present (the reagents employed in this reaction are the same as those used in Rothera's test for acetone.)

Rôle of Glutathione.—The importance of glutathione for tissue oxidation is illustrated by the following observations : (i) Glutathione is absent from the hen's egg ; but after incubation for 36 hours, by which time the embryo has begun to develop and oxidative processes have commenced, a strong nitroprusside reaction can be obtained. (ii) The immature ova and spermatozoa of echinoderms do not give the nitroprusside reaction ; the reaction is positive in ripe eggs and sperm. One minute after fertilization has taken place the nitroprusside reaction is intense ; this increase in glutathione content is associated with an enormous rise in oxygen consumption which is now 8000 times as great as that of the unfertilized ovum.[1] (iii) If yeast is extracted with saline, oxidation in the yeast ceases ; compounds with the —SH group are present in the washings. If the washings or other compounds containing sulph-hydryl groupings are added to the yeast, oxidation is restored. These observations show the importance of sulph-hydryl compounds in oxidative processes.

Some idea of the mode of action of glutathione is obtained by a study of certain inorganic oxidation reactions.

Perfectly dry carbon monoxide and oxygen do not unite to form CO_2 ; but CO and water may give rise to CO_2 in the complete absence of oxygen. The reactions which take place are :

$$CO+H_2O \longrightarrow HCOOH \longrightarrow CO_2+H_2.$$

In the absence of a catalyst this reaction proceeds extremely slowly ; in the presence of palladium black, however, this reaction takes place at room temperature and hydrogen is liberated. It is obvious that the oxygen of the water has been used to oxidize CO to CO_2.

Normally the hydrogen and oxygen of water remain tenaciously united ; but if any substance is present which will take up the hydrogen, the oxygen is left to carry out oxidation. Substances which readily take up hydrogen are called *hydrogen acceptors*, and are now thought to play the predominant part in tissue oxidation.

Palladium black by acting in this fashion speeds up the oxidation of CO in water. Similarly, it enables an aldehyde to be converted into an acid in the presence of water:

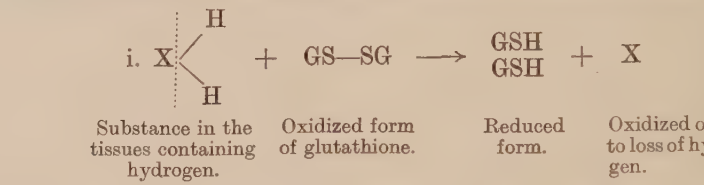
Aldehyde. | Aldehyde hydrate (temporary union with water). | Acid (additional oxygen derived from water). | Which is taken up by palladium.

[1] Shearer, *Proc. Roy. Soc. B.*, 1922, vol. xciii. p. 213.

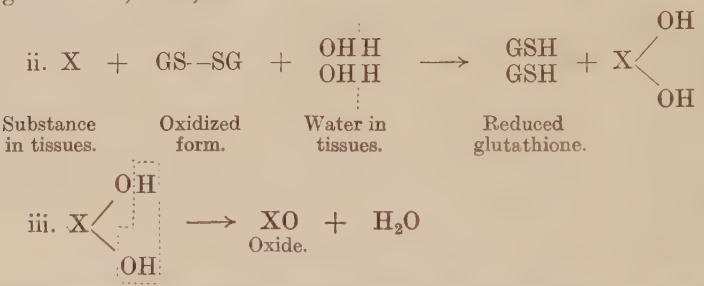
The rôle of palladium in this reaction can be taken by other hydrogen acceptors like methylene-blue or quinone.

The oxidized glutathione of the tissues (GS—SG) probably acts in the same way as palladium black as a hydrogen acceptor. It may accept hydrogen from the tissues, the tissue thus becoming oxidized owing to loss of hydrogen ; or it may unite with the hydrogen of the water, freeing the oxygen of water for oxidation purposes.

The following equations (after Hopkins) illustrate these conceptions :


i. X H H + GS—SG → GSH GSH + X
Substance in the tissues containing hydrogen.
Oxidized form of glutathione.
Reduced form.
Oxidized owing to loss of hydrogen.

GS—SG takes up hydrogen from a substance XH_2 in the tissues, and reduced glutathione, GSH, is formed.


ii. X + GS—SG + OH H OH H → GSH GSH + X OH OH
Substance in tissues.
Oxidized form.
Water in tissues.
Reduced glutathione.
iii. X OH OH → XO + H_2O
Oxide.

Here glutathione acts as a hydrogen acceptor which takes up the hydrogen of *water*. Two OH groupings are left which temporarily unite with the tissue substance X (ii). One molecule of water is then split off and XO is left, *i.e.* the substance X has been oxidized by the oxygen of *water* (iii).

Oxidation of Glutathione. —As a result of the reactions which have been described, glutathione becomes reduced and therefore incapable of assisting further in tissue oxidation ; the reduced glutathione must consequently be restored to its previous oxidized form. In the same way, when palladium black has been in use for some time it becomes saturated with hydrogen and incapable of acting further ; if it is exposed, however, to another hydrogen acceptor, *e.g.* molecular oxygen, the hydrogen is removed and it is restored to its original state. It is found similarly that if reduced glutathione is exposed under suitable conditions to molecular oxygen, hydrogen is removed and oxidized glutathione is re-formed.

$$2GSH \xrightarrow{O_2} GS—SG + H_2O$$

The oxidation of glutathione is obviously of the greatest importance, because it is then restored to the form in which it can accept hydrogen and assist once more in tissue oxidation. Oxidized glutathione may be regarded as an *intermediate* hydrogen acceptor ; it unites temporarily with hydrogen

and then hands it over permanently to molecular oxygen to form water. It is noteworthy that, according to this conception, the oxygen which is supplied to the tissues is only concerned with the conversion of glutathione from the reduced to the oxidized form. Reduced glutathione is said to be *auto-oxidizable* because it is oxidized by molecular oxygen. The reaction takes place readily in an alkaline medium and apparently needs the presence of traces of *iron* to act as catalyst (Fig. 98).

If glutathione is carefully purified, its rate of oxygen uptake is greatly reduced; if minute amounts of iron are added the reaction is accelerated. The process is inhibited by the presence of *cyanide* and other substances which form complex compounds with iron.

As is well known, cyanide is highly poisonous and arrests oxygen consumption in the tissues (p. 462). According to Warburg, the amount of cyanide

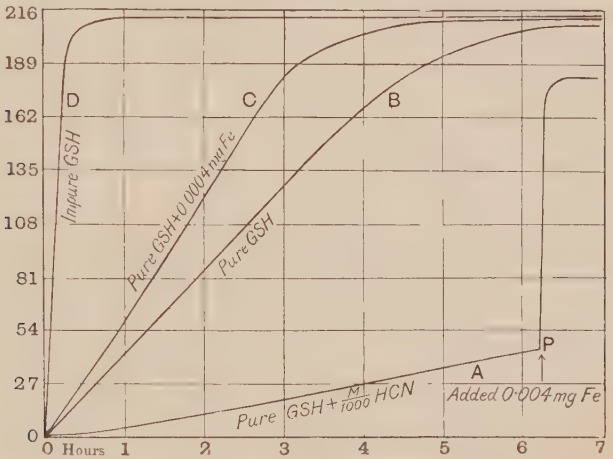


FIG. 98.—Comparison of Rates of Uptake of Oxygen by the following systems: A. 16 mgrms. pure GSH + M/1000 HCN; B. 16 mgrms. pure GSH; C. 16 mgrms. pure GSH + 0·0004 mgrm. Fe; D. 16 mgrms. crude GSH. Ordinate = oxygen uptake in c.cm.; abscessa = time in hours.

which puts a stop to all oxidative activity is just equal to the amount which will unite with the whole of the iron which is present in the tissues. Cyanide exerts its toxic action by preventing the auto-oxidation of glutathione. It is interesting to note that iron also catalyses other oxidative processes; for example, pure lecithin takes up no oxygen, but in the presence of iron oxygen is used.

Salvarsan.—It has been suggested by Voegtlin that salvarsan produces its effects by uniting with the glutathione of the spirochætes and arresting their oxidative activities. If salvarsan is injected together with glutathione in suitable doses, no toxic symptoms result in experimental animals. It must be presumed that the spirochætes are more susceptible than the cells of the host to this action of salvarsan.

3. **Thermostable Substance.**—Glutathione appears to act in conjunction with a substance in the tissues which is thermostable and resists heating to 100° C. (Hopkins and Dixon).

Glutathione or washed fresh muscle *alone* takes up relatively little oxygen. The combination of the two enables respiration to occur rapidly. The thermostable substance in the system can be replaced by the lecithine fraction of an alcohol-ether extract of muscle ; so the essential adjunct may be an unsaturated fatty acid. It may be pointed out that glutathione accelerates the oxidation of oils like cod-liver oil, which contain unsaturated fatty acids.

4. **Rôle of Nucleus and Cell Structure.**—If the nucleated red cells of birds are frozen and thawed, hæmolysis occurs. As a result of centrifuging, an upper layer of structureless cell substance and a lower one of structural elements and nuclei are obtained. The lower nucleated layer alone continues to consume oxygen. If the juice is pressed out of these red cells or if they are mechanically disintegrated, oxygen consumption ceases. If cells are killed with acetone, which leaves the original structure unchanged, small amounts of oxygen continue to be used for some time.

Clearly many factors have to be considered in discussing tissue oxidation. Oxidases, hydrogen transport by means of glutathione, some unknown thermostable substance (possible unsaturated fatty acid), iron, the structure of the cell, and its nucleus all play some part. We have mentioned previously that certain internal secretions, particularly thyroxine (p. 155), adrenaline (p. 129), and the products of protein hydrolysis (p. 320) stimulate tissue oxidation. (See also p. 339 for importance of oxygen pressure.)

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DYSPNŒA

Definition — Vital capacity — Mechanical efficiency — Dyspnœa from increased metabolism—From disturbed blood reaction—From oxygen lack—From mechanical and nervous hindrances—Obstruction to air-passages—Orthopnœa —Cardiac dyspnœa.

Definition.—Normally, breathing goes on without intruding on consciousness. Dyspnœa literally means difficult breathing. Meakins defines it as "consciousness of the necessity for increased respiratory effort." If the breathing enters consciousness unpleasantly and produces discomfort, it becomes dyspnœa. *Hyperpnœa* simply means increased breathing and for a time does not impinge on consciousness, and so it is a stage preceding the onset of dyspnœa. An ordinary person is not aware at all of any increase in the breathing until the pulmonary ventilation is doubled. Real discomfort develops when the ventilation is increased four- or five-fold. This level of ventilation is called the "dyspnœa point" Dyspnœa is not wholly a pathological phenomenon, for, as noted (p. 362), dyspnœa develops in normal subjects during strenuous exertion.

During muscular activity the metabolism and the breathing both increase

proportionately. The amount of work which will produce dyspnœa in a normal subject depends on several factors.

1. **Vital Capacity.**—During exercise the breathing becomes deeper as well as more rapid. It has been found (Peabody) that the closer the depth of the breathing approaches the vital capacity of the individual, the greater is the subjective discomfort which is experienced. Other things being equal, people with a lower vital capacity tend to become dyspnœic when doing less work and with lower grades of hyperpnœa.

2. **Mechanical Efficiency.**—Training improves the co-ordination of the muscles, eliminates wasteful and superfluous movements, and enables any given task to be carried out with a minimum expenditure of energy. The mechanical efficiency of an athlete is 25 to 30 per cent. (p. 358), *i.e.* over one-quarter of the total energy output of the body is converted into work. In an untrained person the mechanical efficiency is only 20 to 23 per cent., so that to do the same amount of work he must liberate more energy, and consequently his oxygen consumption and pulmonary ventilation are proportionately greater than in an athlete. He therefore develops dyspnœa earlier. The efficiency of the respiratory muscles themselves is also less good in the untrained person, and so the respiratory movements are not carried out easily and quickly. The fatigue which develops in these muscles may contribute to the general respiratory discomfort which constitutes dyspnœa.

3. **Rate of Diffusion** of oxygen through the lungs varies in different individuals according to the permeability of the pulmonary epithelium. If the permeability is poor, it is possible that the blood-flow through the lungs in severe exercise may be too rapid to permit of complete arterialization of the blood. The nutrition of the respiratory centre suffers, it becomes fatigued, and the respiratory movements cannot be carried out without a sense of effort.

The ventilation in an untrained person therefore increases more markedly than in an athlete (because of his lower mechanical efficiency), and the dyspnœa point is lower (because of the smaller vital capacity).

Pathological Dyspnœa.—The causes of dyspnœa may be classified as follows (Means) :

1. From Increased Metabolism.—Patients with *exophthalmic goitre* have a higher rate of metabolism at rest, and therefore their resting pulmonary ventilation is 50 to 100 per cent. above normal, depending on the severity of the case. The vital capacity is found to be low in this condition, and the mechanical efficiency is lower than normal, *e.g.* only about 15 per cent. (Plumer and Boothby). No dyspnœa is present as a rule at rest ; but when doing work they are handicapped in several ways. They commence with a high resting pulmonary ventilation ; being inefficient machines, their ventilation increases very steeply, as they have to liberate an excessive amount of energy to perform any task ; owing to their low vital capacity, subjective symptoms arise when the hyperpnœa is yet moderate. In some cases, cardiac irregularity (auricular fibrillation) or heart failure is an additional factor to be considered.

2. From Disturbed Acid-Base Equilibrium. — i. Some cases of *nephritis* show a definite increase in the H ion concentration of the blood, owing, it is thought, to the failure of the kidney to excrete adequately non-

volatile acids. The respiratory centre is therefore stimulated and the ventilation may reach the dyspnœa point. The increased breathing is an attempt to restore the cH of the blood by washing CO_2 out of the blood, and the CO_2 tension in alveolar air and arterial blood is consequently very low. In one uræmic patient with a blood urea of 332 mgrms. per 100 c.cm., the pulmonary ventilation was 51 litres, the alveolar CO_2 6·4 mm. Hg, and the bicarbonate content of the blood 12 volumes per cent. (Means and Rogers). The administration of alkali in adequate amounts temporarily restores the normal cH of the blood and abolishes the hyperpnœa or dyspnœa and the coma which may have been present. There is not, however, a constant ratio in nephritis between the degree of acidæmia and the pulmonary ventilation, as the *sensitivity* of the respiratory centre may be depressed by the disease.

ii. *Ingestion* of substances which give rise to acids in the body, *e.g.* methyl alcohol (which is converted into formic acid) and ammonium chloride (which liberates HCl) (p. 322), may produce dyspnœa.

iii. *Diabetes.*—In a severe case of diabetes the abnormal acids formed from incomplete fat metabolism break up the bicarbonate of the plasma. Compensatory hyperpnœa results, to lower the alveolar and arterial CO_2 tension (p. 419). The breathing is slow and deep but easy, and the pulmonary ventilation is rarely increased fivefold, *i.e.* to the dyspnœa point. When the breathing is truly laboured, coma is usually present, and strictly the condition can no longer be called dyspnœa. Both the deep breathing ("air-hunger") and the loss of consciousness which characterize diabetic coma are mainly to be attributed to the poisonous enol grouping in aceto-acetic acid (p. 421).

3. From Oxygen Lack.—The question of anoxæmic stimulation of the respiratory centre has already been fully discussed (p. 323). The *anæmic* and *stagnant* forms of anoxæmia tend to produce little dyspnœa, as the oxygen tension in the arterial blood is normal. In the *anoxic* form the respiratory centre is stimulated by the subnormal oxygen tension in the blood; and if adequate time is allowed for compensaton to be established, the breathing may be very greatly increased (p. 324).

4. From Mechanical and Nervous Hindrance to the Respiratory Movements.—(1) *Reduced Vital Capacity.*—This is present in exophthalmic goitre (p. 310), in heart disease (p. 372), and in many diseases of the lungs and pleura, *e.g.* pneumonia, hydrothorax, pneumothorax, and thoracic tumours. In cases of chronic *pneumothorax*, for example, the breathing at rest is quite comfortable. In response to exercise or to excess of CO_2 in the inspired air, the breathing increases in a normal manner, but intense dyspnœa is present when the ventilation has increased only threefold. This is due to the diminished vital capacity which results from one lung being largely thrown out of action. The depth of the breathing soon approaches the limited vital capacity, and so dyspnœa develops early.

In *asthma* bronchial constriction is present which diminishes the vital capacity and prevents the easy passage of air in and out of the lungs. During an acute attack, the vital capacity is so limited by the bronchial spasm, and the effort needed to displace air from the lungs is so great, that intense dyspnœa is present.

Paralysis of the *diaphragm* or interference with its action by great

abdominal distension produces more embarrassment when it is of sudden occurrence than if it is gradually produced. Here again the vital capacity is diminished.

In *emphysema* (i) the lungs are excessively distended at rest, and are permanently in the inspiratory position, thus reducing the vital capacity ; (ii) the bronchial musculature is atonic, and much of the air which enters during inspiration serves merely to distend the bronchi instead of entering the alveoli ; (iii) it has been found, too, that the respiratory centre in this condition has an increased tolerance to CO_2 : the breathing increases to a less extent than normal when air containing excess of CO_2 is inspired. Consequently, the amount of CO_2 which is produced in the body does not produce an adequate degree of ventilation, and so the blood is not fully oxygenated. (iv) Further, the pulmonary capillaries are compressed and many of them are obliterated by the distended alveoli, and this further interferes with gaseous exchanges. Arterial anoxæmia, the shallow breathing associated with oxygen lack, and *cyanosis* are thus present (pp. 340, 346).

(2) *Obstruction to Air-Passages.*—When the resistance is slight, the breathing becomes slower and deeper. If the resistance is excessive, and continues for a long time, the respiratory centre becomes fatigued and the breathing becomes increasingly shallow and more frequent. The alveolar ventilation becomes inadequate in consequence, and arterial anoxæmia develops, which aggravates still further the depressed state of the centre.

When the air-way is free, the hyperpnœa of exercise can be maintained for a long time, but when the breathing is obstructed, the fatigued and badly nourished respiratory centre cannot keep up the hyperpnœa of work in the normal manner.

If the trachea is *obstructed* in any phase of the breathing, the *initial* reaction is an expiratory or inspiratory effort, depending on whether the lungs are left full or empty. As no air currents are passing up or down the bronchioles, the vagal nerve endings are not stimulated. The result is the same as if the vagi had been cut (cf. p. 328), *i.e.* the breathing becomes for a short time slow and deep. As the respiratory centre is not receiving any vagal impulses, its own inherent rhythm is revealed. Later, hyperpnœa and intense dyspnœa develop owing to accumulation of CO_2 and oxygen lack. Similarly, if a man is allowed to breathe into a bag containing air under pressure, the lungs are distended, and a prolonged expiratory effort results which finally succeeds in emptying the lungs. The breathing is at first slow, because of the resistance, but gradually quickens as the respiratory centre is stimulated by the accumulation of CO_2 in the lungs, which is produced by the initially inadequate breathing.

(3) (*a*) Shallow rapid breathing occurs in neurasthenia and other functional nervous disorders. The respiratory centre is probably in a depressed state, and so responds more readily to the vagal impulses from the lungs, which check the depth of the breathing excessively.

Dunn produced multiple embolism of the pulmonary arterioles by intravenous injection of starch granules. With a moderate degree of embolism insufficient to produce death, there is great increase in the frequency and diminished depth of respiration to half or one-quarter normal. If the vagi are now divided, slow and normally deep respiration develops. The dis-

turbed pulmonary circulation thus produces an exaggerated vagal reflex, which at first may even cause complete arrest of the breathing. How the vagal nerve endings are excited in this condition is not certain.

(*b*) Failure of the respiratory centre may occur at night, when the centre is depressed (p. 330); the patient feels he cannot expand his chest to breathe. This is followed by very frequent shallow breathing—so-called "*paroxysmal dyspnœa.*" Haldane suggests this is due to the depressed centre being affected to an excessive degree by vagal impulses from the lungs, which may first arrest the breathing momentarily, and then check the depth excessively (cf. Dunn's experiment, p. 371).

Orthopnœa is a condition in which patients are exceedingly uncomfortable and short of breath in the recumbent position, and find it essential to be propped up in bed or in a chair. When a normal person lies down, the breathing becomes slower and deeper. This is probably due to the ordinary slowing effect of resistance to the breathing—increased resistance is thrown on the diaphragm by the necessity to move the liver and other abdominal organs. An enfeebled respiratory centre, owing to the malnutrition resulting from a failing circulation, is unable to inaugurate movements of adequate depth when the body is in the recumbent position. The breathing consequently becomes excessively shallow, and dangerous anoxæmia may develop. In the erect position, diaphragmatic movements are aided by gravity, and adequate alveolar ventilation can be maintained (Haldane).

5. CARDIAC DYSPNŒA.—(1) In cases of heart disease in which an adequate circulation is maintained the metabolic rate is normal. When heart failure develops the metabolism for some unknown reason is often raised by 25 to 50 per cent. above normal. This, of course, means that the pulmonary ventilation at rest must be correspondingly increased.

(2) There is a subnormal circulation rate, because of leakage through valves, obstruction at the cardiac orifices, congenital communications between the two sides of the heart, or an enfeebled myocardium. Less blood is consequently supplied to the tissues, with the result that *stagnant* anoxæmia is present. If œdema of the lungs is present, or if emphysema is a complicating factor, *anoxic* anoxæmia develops from imperfect oxygenation of the blood passing through the lungs. As would be expected, one consequently finds in some cases rapid shallow breathing with lowered alveolar CO_2 tension and an *alkalœmia* of the arterial blood, consequent upon stimulation of the respiratory centre by oxygen lack (Fraser, Ross, and Dreyer). This shallow rapid breathing is ineffective and tends to aggravate still further the anoxæmia which is present.

(3) In some cases CO_2 cannot be normally eliminated from the lungs because of the altered condition of the pulmonary epithelium. The CO_2 content of the blood is therefore raised, and the tendency to acidæmia is a contributing factor in stimulating the respiratory centre (Campbell, Hunt, and Poulton).

(4) The vital capacity is diminished in heart disease when circulatory failure has developed, because of the congested state of the pulmonary vessels, the loss of the normal elasticity of the lungs, and complications like hydrothorax. It is found that when the vital capacity is 70 to 90 per cent. of the normal, the patient is still able to do work, but dyspnœa develops on exertion; when it is 40 to 70 per cent., very little work can be done; when

it is below 40 per cent., the patient is usually bedridden, with marked signs of cardiac insufficiency.

The picture is thus a very complex one. The main points to remember are—(i) Raised metabolic rate at rest; (ii) diminished vital capacity; (iii) anoxæmia and consequently a malnourished respiratory centre; (iv) CO_2 accumulation at times and acidæmia. With all these disabilities it is not surprising that dyspnœa occurs during moderate work, and even at rest when the lungs themselves are involved. Secondary renal failure may complicate the issue, causing retention of non-volatile acids, especially in the "cardio-renal" type common in elderly subjects.

6. Cheyne-Stokes Breathing (p. 327).

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TEMPERATURE REGULATION

Normal findings—Diurnal variation—Effects of age, exercise—Surface temperature—Temperature regulation—Influence of nervous system—Response to cold and heat—Climatic conditions and clothing—Heat stroke—Fever.

Normal Findings.—The normal range of temperature is as follows:

Mouth	96·7° to 99° F.
Rectum	97·2° to 99·5° F.

Rectal Temperature is the highest and the most reliable. It is at least 0·5° to 0·75° F. higher than the mouth temperature; after exercise the difference may be greater.

Mouth.—The thermometer must be kept in the mouth for at least ten minutes to get a really reliable reading of the internal temperature of the body; if the nose is blocked, the reading is of little value. Mouth temperature is liable to variations from *local* conditions, *e.g.* it is cooled by evaporation of sweat and contact with cold air. Hot drinks at the usual temperature (120° to 140° F.) may raise the mouth temperature above that in the rectum. The activity of the muscles of mastication and the consequently increased blood-flow through them (and through the salivary glands), which occurs during a meal, has the same effect. In warm surroundings, shielded from the cold, *e.g.* in bed, the buccal temperature may almost equal the rectal.

The temperature in a stream of *urine* is 0·3° to 0·5° F. below rectal. The temperature taken in the *axilla* and *groin* is inaccurate in thin subjects; otherwise it approximates to the buccal (0·4° F. below rectal).

In any individual the daily temperature range in health is 1° F. and may reach 1·5° F. In the tropics the temperature is about 1° F. above normal.

On cold mornings it may be slightly subnormal. In nervous people, and especially in children, elevations of temperature occur for no adequate cause.

During *menstruation* the temperature is at a minimum. It rises slightly during the next 14 days. It reaches its maximum in the premenstrual period, to fall again with the onset of menstruation. The difference between the minimum and maximum readings is 0·3° F. (Cullis).

The effect of food on the *mouth* temperature has been noted. The ingestion of food stimulates the metabolic activities of the body and may raise the *internal* temperature by 0·2° to 0·3° F.

Diurnal Variation.—The temperature is highest in the evening and lowest in the early hours of the morning. The time of the maximum temperature is usually between 5 and 8 p.m., but varies in different individuals. In a case of suspected phthisis two-hourly records should first be taken to discover the time of the maximum temperature, and that hour should subsequently be used for the evening reading.

The normal variation is due to the degree of *muscular activity* which occurs by day. A reversal of the ordinary daily routine, as in night workers, reverses the temperature curve. This does not occur during the first night, for at 4 a.m., the hour of the usual minimum, there is an imperative desire to sleep. After a few days, acclimatization takes place and the sleepiness passes off.

When a healthy man is kept in bed the normal temperature variations take place, but the evening maximum is not so high. During *sleep* the temperature falls because of bodily inactivity and diminished control of temperature regulation which shows itself in vaso-dilatation of skin vessels, sweating. Sweating may be normal in sleeping children and adults.

Age.—The temperature in *infants* is irregular at first, but periodicity gradually sets in with the development of regular periods of activity and rest. Heat regulation is imperfect—a fit of screaming causes a rise ; a cold bath may lower the temperature by 7° F.

In *old* people the temperature is subnormal. The body is less active, the circulation is feeble, and there is less power of accommodation for changes in external temperature. They tend to suffer in extremes of temperature.

Exercise.—After a three-mile race temperatures of 103·6°, 103·8°, and 105° F. have been recorded in athletes. When two, four, and six miles are covered in one hour's walking the temperature may rise 1°, 2·1°, and 4·3° F. respectively. The rise is proportional to the exertion which is made, and is due to the heat liberated in the active muscles (p. 357). It is unaccompanied by any ill effects or feeling of discomfort. It helps to increase the breathing and the pulse-rate, and facilitates the dissociation of oxyhæmoglobin in the tissues (p. 332).

In *pulmonary tuberculosis*, the increased blood supply through the lungs which accompanies bodily activity results in the washing away of toxins from the foci of disease into the general circulation. Exercise in such patients produces an excessive rise of temperature which is due in part to the work done, and in part to toxic absorption—and this is of value in diagnosis.

An afebrile phthisical patient and a normal control were allowed to walk up a slight incline of $3\frac{3}{4}$ miles in $1\frac{1}{4}$ hour. The average rise of temperature (rectal) in the control was 0·97° F., and in the patient 1·6° F.

In practice an attendant of known physical soundness and the suspected subject do exactly the same work, and the rise of rectal temperature is compared in the two cases.

Surface Temperature. — To determine the surface temperature a mercury thermometer with a flat bulb is used. It varies considerably in different parts. This absence of uniformity is a sign of well-being. As soon as a uniform surface temperature develops, discomfort results. Conditions which influence skin temperature are (i) external, *e.g.* temperature, moisture, wind, clothing ; (ii) internal, *e.g.* muscular work.

Temperature Regulation. — Temperature regulation is effected by balancing heat production against heat loss.

Heat *loss* occurs (i) by conduction and radiation ; (ii) by evaporation of moisture from the skin and lungs ; (iii) in the excreta (urine and fæces). The loss in the excreta is trivial : 25 per cent. is lost by evaporation and the rest by conduction and radiation.

Heat *production* takes place mainly in the skeletal muscles, and to a less extent in the glands, particularly the liver and kidney. The metabolic activities of the body at rest, *i.e.* the rate of oxidation in the tissues, are so adjusted as to maintain the appropriate internal temperature ; it is stated (de Almeida) that in the tropics the heat production at rest is only about 30 C. per sq. metre compared with 40 C. per sq. metre in temperate zones. Conversely the metabolism is stimulated by external cold.

The vascularity of the skin, the activity of the sweat glands, the pulmonary ventilation, the activity of skeletal muscles, and the secreting glands are all under the control of the nervous system. Impulses arise in the temperature sense organs and initiate a series of reflex responses which tend to maintain the body at the optimum temperature. The nerve centres are also affected directly by the temperature of the blood which bathes them. Warming the blood in the carotid artery results in the manifestations of heat loss, *e.g.* cutaneous vaso-dilatation and sweating.

Influence of Nervous System.—After removal of the *cerebrum* in a dog, normal temperature regulation is preserved but is limited in range. The animal responds appropriately to external heat and cold, but it cools down if left for a long time in a cold room. Evidence has been given that the temperature controlling centre is probably situated in the hypothalamic region, possibly in the vicinity of the tuber cinereum (pp. 152 and 83).

A *midbrain* preparation is cold blooded (poikilothermic) in its behaviour. As a result of injuries to the *pons* and *medulla*, a rise or fall of body temperature may result. It is usually stated that pontine hæmorrhage leads to hyperpyrexia. This is not constantly the case, however. The greater part of the body is paralysed and is cut off from the influence of the heat-regulating centres, and therefore follows passively the temperature of the surroundings. If the weather is warm, the room overheated, and the patient well wrapped up and surrounded with hot bottles, the temperature of the paralysed regions rises. No sensory impulses can pass up from this region to the centres at the base of the brain, nor can efferent impulses reach the affected muscles or blood vessels. The temperature of the whole body rises. Similarly, if the paralysed regions are cooled, the general temperature falls (Pembrey).

In the *denervated* limb the temperature rises at first, as, owing to loss of

vasomotor tone, more blood passes through the dilated arterioles. A few days later the paralysed limb is colder. The vessels have now regained their independent tone ; the venous return is impaired owing to paralysis of the skeletal muscles, and so the blood tends to stagnate in the part.

To summarize : If the central nervous system is depressed as by the action of anæsthetics, or grossly injured in essential parts by lesions like hæmorrhage, or if integral parts of the heat-regulating mechanisms are paralysed, *e.g.* the skeletal muscles by curare, this complex and delicately co-ordinated function fails, and alteration of body temperature results.

The power of regulating temperature gradually makes its appearance in the evolutionary scale. A premature infant cools at ordinary room temperature and must be kept artificially warm by incubation. A full term infant shows considerable fluctuations of temperature and cannot resist exposure to cold. The nervous system does not assume full integrated control over the muscles, blood vessels, sweat glands, etc., for some little while, in the same way as other complex co-ordinated activities take time to develop. A healthy infant a few months old does not require artificial warmth if it is properly clothed and fed.

Response to Cold.—If the external temperature *falls* below 14° C. the metabolism is stimulated to increase heat production. It has already been pointed out that this reaction is due partly to secretion of adrenaline which increases tissue oxidation and partly to increased muscular activity (p. 132). A cold bath may increase the metabolism by 80 per cent. (Lusk). The cutaneous arterioles are constricted to diminish heat loss and the blood is driven into the deeper parts of the body, especially to the abdominal organs and brain. The blood pressure may rise. It has been suggested that the fluid part of the blood which is removed from skin vessels is stored in the muscles and other tissues, so that the hæmoglobin percentage and the red blood count may be increased.

Response to Heat.—If the external temperature is *raised*, dilatation of the cutaneous arteries results, so that a greater volume of blood is exposed to the outside air. Loss of heat by conduction and radiation is thus facilitated. The volume of the abdominal organs and brain is diminished, and the blood is accommodated in the skin vessels. The circulation rate is increased (p. 265). The blood leaving the skin veins is highly saturated with oxygen —*i.e.* the increased blood supply to the skin is determined by requirements of temperature regulation and not as usual by tissue activity.

Sweating takes place and heat loss occurs as a result of evaporation. A distinction may be drawn between "invisible perspiration," which is possibly a transudate from the blood vessels, and "sweat," which is secreted in beads and is associated with increased CO_2 output by the skin. The secretion of sweat is partly reflexly elicited by impulses arising in the temperature sense organs in the skin, and is partly due to a rise in the temperature of the blood supplied to the brain. CO_2 excess and oxygen lack (as in partial asphyxia), the anæsthetics, and certain poisons may also produce sweating. It must be remembered that loss of heat by radiation and conduction can only occur if the external temperature is lower than that of the body ; if it rises higher the only method of heat loss available is by means of evaporation. In a man without sweat glands the internal temperature rose to 102·2° when doing work for a short time. His cutaneous vessels dilated normally, but

this mechanism alone was inadequate ; he therefore had to soak his shirt repeatedly in cold water (Pembrey).

During exposure to dry heat in a Turkish bath for 2½ hours, 2·3 kgrms. in weight was lost, almost entirely in the sweat (Hunt). Though no liquid was drunk the percentage hæmoglobin was the same before and after the experiment, so that no concentration of the blood had occurred. It is believed that fluid oozes out from the muscles and the tissues generally to compensate for the loss which is occurring in the sweat. This is due to (i) the raised osmotic pressure of the plasma proteins which attracts fluid from the tissue spaces ; (ii) the central nervous system acting on the tissues in some ill-understood way. In this way reserves of fluid from the tissues are mobilized effectively to withstand the loss of even several litres of water from the skin. It is essential, however, to replenish these reserves by copious drinking.

The *pulmonary ventilation* is increased (cf. p. 325). As the expired air is saturated with water vapour loss of heat is increased by this means.

Importance of Climatic Conditions and Clothing.—Heat loss is diminished if the outside air is still, because the body is then surrounded by a layer of warmed air. Moist air is a better conductor of heat than dry air, and increases the loss by conduction and radiation though less evaporation can occur. A cold damp day is more intolerable than a cold dry day. A warm moist day is unpleasant, as evaporation is interfered with.

About 20 to 30 litres of air are entangled between the clothes. This is helpful in cold weather by diminishing heat loss by radiation and conduction. In hot weather the clothes retain moisture and the cooling effect of sweating is diminished. Evaporation takes place from the surface of the clothes and only affects the skin through a layer of damp undergarments. Opening the jacket, waistcoat, and shirt gives, as is well known, a feeling of greater comfort, and more moisture can evaporate from the skin surface.

If the external temperature is raised, and the air is moist and still, the regulating mechanism may break down. Thus in a dry room at a temperature of 240° to 260° F. no rise of body temperature occurred ; 15 minutes in a *moist* room at 130° F. raised the temperature in the mouth and urine to 100° F.

Haldane, attired in flannel drawers, canvas trousers, boots, and stockings, remained for 2¼ hours in a "level" in the Dolcoath mine in Cornwall. The dry bulb temperature was 94° F. and the wet bulb was 93·6° F., *i.e.* the air was highly saturated with moisture, and there was no ventilation. No work was done and yet there was much general discomfort. The pulse-rate rose to 164 per minute and the rectal temperature to 104·2° F.

If the wet bulb temperature is 85° F. the rectal temperature remains normal when the subject is at rest in still air. If the wet bulb shows a rise of 1° F., the rectal temperature rises markedly. At 89° to 90° the rise of body temperature was 1° to 1·4° F. per hour ; at 94°, to 2° per hour ; at 98°, to 4° per hour. In moving air, *i.e.* an air current of 50 metres per minute, a wet bulb temperature of 93° F. was borne without rise of internal temperature.

If muscular work is done in still air, the limit of wet bulb temperature is still lower. During leisurely climbing it is 78° F., but if the work is harder the limit is lower still. As the body temperature rises the symptoms are as follows :

1. Great increase in the pulse-rate—20 per minute for each 1° F. rise in rectal temperature when standing, or 15 per minute at rest.

2. Hyperpnœa develops, which is noticeable when the temperature is 102° F. and becomes distinct over 103° F. The alveolar CO_2 falls (p. 325). Great dyspnœa develops during work.

3. There is general exhaustion and a feeling of discomfort.

Heat Stroke is a disorder of temperature regulation which occurs in men who are working hard, unsuitably clothed, in conditions of moist heat. As the external temperature is high, heat loss by means of conduction and radiation ceases. If the air is moist and still, evaporation is also hindered. When the heat-regulating mechanism breaks down, the body temperature rises. This stimulates metabolism (p. 319) and heat production is further increased. A vicious circle is thus established with ever-rising body temperature and increasing metabolism. Individual idiosyncrasy is important; some men do not sweat readily—their skin is hot and burning, but quite dry. The peripheral vaso-dilatation tends to lower the blood pressure and interferes with the cerebral circulation. The heart is affected by the raised temperature and the deficient blood supply, and its failure may be the cause of the collapse in some cases. Severe and even permanent injury to the central nervous system may occur.

Exposure to Cold.—As a result of fatigue an individual wandering in the cold surrenders to an overpowering desire to sleep. During this unconscious state temperature regulation is disturbed and much heat is lost. The body temperature falls; at 68° F. coma sets in and death results. It has been pointed out (p. 297) that a fall of body temperature depresses the dissociation of oxyhæmoglobin and tends to lower oxidation in the tissues.

"**Fever**" is a term used to describe the complex response of the body to infection. One of these manifestations is *pyrexia* or raised temperature. The body is able to deal more effectively with the invading organisms when the temperature is raised, and so the pyrexia must be regarded as a protective mechanism. Increased heat production and diminished heat loss are present. This alone does not account for the pyrexia, because the changes are of an order of magnitude which can be easily compensated for normally. Heat regulation is therefore *disordered*; the body is adjusting its temperature to a higher level than normal. Heat regulation is not entirely lost, however; the normal diurnal variation is still present, and the patient responds in the usual way to applications of heat and cold.

In the *initial* stage a rigor or shivering often occurs. The skin vessels are constricted, minimising heat loss. A rapid rise of temperature therefore takes place. During the *fastigium*, when the temperature is at its height, the cutaneous vessels are relaxed and the skin is flushed. The sweat glands are usually paralysed. The rise of temperature increases the metabolic rate (p. 319) by accelerating the oxidative activities of the body. The toxins of the disease may directly cause increased tissue breakdown. The heat loss is relatively inadequate to cope with this increased production. During the *defervescence*, when the temperature falls, marked sweating occurs, and heat loss is now greater than heat production.

The other manifestations of fever are due partly to the pyrexia and partly to the action of toxins. The nervous symptoms are restlessness, depression, or delirium. There is loss of appetite and diminished intake of

food. Because of the small residue in the bowel and the poisoned condition of the muscle wall, constipation is present. There is increased nitrogenous excretion in the urine owing to increased metabolism, the destructive changes caused by the toxins, and increased tissue breakdown to provide energy because of the state of semi-starvation. The pulmonary ventilation and pulse-rate are increased. The blood pressure is raised at first, but falls later. The flow of urine is scanty

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VIII

THE DIGESTION

SECRETION OF DIGESTIVE JUICES

Saliva—Gastric juice—Methods—Fractional test meal—Continuous secretion—Appetite juice—Response to food—Gastrin—Secretion in man—Interpretation of curves of acidity—Composition.

Pancreatic juice—Vagus—Secretin—Composition—Action—Succus entericus—Large intestine.

Bile—Pigments—Bile salts—Origin, functions, circulation—Cholesterol—Metabolism and functions—Functions of gall-bladder—Cholecystography—Gall-stones—Complete extirpation of liver—Carbohydrate metabolism—Nitrogenous metabolism—Relation to blood—Partial extirpation.

Secretion of Saliva.—The innervation of the salivary glands is described on pp. 120, 124. The sympathetic fibres reach the glands along the coats of the blood vessels, the excitor cell station being in the superior cervical ganglion. The *parotid* gland receives parasympathetic fibres from the inferior salivary nucleus along the glosso-pharyngeal nerve ; the excitor cell station is the otic ganglion which sends post-ganglionic fibres in the auriculo-temporal nerve to the gland. The *submaxillary* and *sublingual* glands receive parasympathetic fibres from the superior salivary nucleus through the pars intermedia and chorda tympani ; the relay station is in nerve cells which lie in the vicinity of the glands.

The parotid gland secretes a watery juice which is chiefly used for moistening the food. The submaxillary and sublingual glands produce a sticky juice which is rich in mucus.

According to Heidenhain the sympathetic fibres are *trophic* nerves which produce a specific change in the gland leading to the formation of the ferments contained in the secretion. Stimulation of the sympathetic is said to produce histological changes in the parotid gland and constriction of the arteries. The parasympathetic fibres are *secreto-motor—i.e.* they cause the secretion of salts and water, and dilatation of arterioles. Secretion of saliva is produced reflexly as a result of the taste, sight, thought, or smell of food.[1]

Œsophago-Salivary Reflex.—Roger showed that if the œsophagus is cut and its distal portion is stimulated, an abundant flow of saliva results. This reflex depends on the integrity of the vagi. The importance of this reflex is that it enables us to wash forward any bolus which is held up in the

[1] For discussion of the changes which take place in these glands during activity, see p. 303.

œsophagus. Peristalsis cannot be initiated in the œsophagus as a result of mechanical stimulation ; but when the reflexly secreted saliva is swallowed, it sets up the processes of deglutition which result in co-ordinated contraction of the œsophagus and the bolus is moved on. In *carcinoma* of the œsophagus, salivation, reflexly produced in the way described, is a common symptom.

Gastro-Salivary Reflex.—If food is introduced into the stomach of a dog with precautions to avoid psychic impressions, a flow of saliva occurs after an interval of twenty minutes.

Secretion of Gastric Juice.—The following experimental methods may be employed to investigate the secretion of gastric juice :

In Animals.—1. *Stomach Pouch.*—The method of Pavlov may be employed in which a small pouch of the stomach is separated from the main body of the organ by a double layer of mucous membrane and the open end is brought up to the surface of the body. The nervous and vascular connections of the pouch are left intact. Pure gastric juice unmixed with food can be obtained from the pouch while the digestive processes are proceeding in the main stomach (Fig. 99 b).

2. *Sham Feeding.*—The œsophagus is exposed in the neck and divided, and the two cut ends are brought up to the surface. " Sham feeding " or drinking can now be carried out—*i.e.* food is given which is masticated and swallowed, but drops out through the upper end of the cut œsophagus. Food can also be introduced directly into the lower end of the cut œsophagus and thus reaches the stomach without the animal being aware of it.

3. *Stimulation of the Vagus.*—Under anæsthesia, the vagus nerve is exposed in the neck and divided. A few days are allowed to elapse for the cardio-inhibitory fibres to degenerate ; the fibres which pass to the stomach survive longer. The peripheral end of the cut vagus may then be stimulated and the effects noted. An immediate flow of gastric juice results, proving the vagus to be the secretory nerve to the stomach.

In Man.—1. *Fractional Test Meal.*—A fine flexible rubber catheter is swallowed first thing in the morning, no food having been taken since the previous evening. The *resting contents* of the stomach are aspirated with a Record syringe. The stomach is washed out with distilled water which is withdrawn. A pint of thin gruel is swallowed and 10 c.cm. of gastric contents are aspirated at intervals of fifteen minutes until the stomach is empty.

Analysis.—To 5 c.cm. of gastric contents a few drops of Töpfer's reagent (dimethyl diamido azo benzol) are added. A bright red colour indicates the presence of *free HCl*. Titrate with $N/_{10}$ NaOH till the solution becomes lemon-yellow. (Multiply the figure obtained by 20 to get the amount of $N/_{10}$ NaOH which neutralizes 100 c.cm. of gastric contents.) Add a drop of phenol-phthalein, and run in more NaOH till the solution goes pink. This figure multiplied by 20 gives the *total acidity*.[1] The difference between the free HCl and total acidity is a measure of the HCl which is organically combined with mucin and protein, and of any abnormal acids like lactic acid, which may be present. In addition, the *total chloride* content may be determined ; this represents the sum of the free and combined HCl and the *inorganic chloride* ; the last is probably mainly produced by neutralization

[1] The term "active" HCl is used in Figs. 100-103 to denote free HCl + HCl combined with protein.

of the gastric HCl by alkali, which has regurgitated from the small intestine. The results are plotted in the form of a curve (Figs. 100–103, and p. 385).

2. In cases of *gastric* fistula in man, as a result of injury or operation, the gastric mucosa may be inspected and gastric juice directly obtained.

Continuous Secretion by Fasting Stomach.—It has been found in healthy individuals with gastric fistulæ, that the stomach in the absence of food secretes gastric juice at the rate of 10 to 60 c.cm. per hour. Similar results are obtained by means of the stomach tube. The secretion is not uniform in rate, but the variations are less marked than those shown by the motor phenomena of the empty stomach. This continuous secretion persists throughout prolonged fasting, but decreases in quantity unless NaCl is given in the drinking water to make up for the loss of chloride in the gastric juice. The mechanism of fasting secretion is unknown; it persists after double vagotomy.

Appetite Juice.—If the vagi are intact, the sight, smell, or taste of food reflexly produces a flow of gastric juice. The secretion thus obtained is called the *psychic* or *appetite* juice. Taste is the most effective stimulus; the sight and smell of food often produce no result. Chewing indifferent substances not related to food is ineffective. If sham feeding is carried out in a *dog* for five minutes after a twenty-four hours' fast, a secretion is obtained (after a brief latent period), which persists for as long as four to six hours. In *man*, appetite juice is relatively unimportant, possibly because under civilized conditions real hunger is rarely experienced. If a meal is chewed and spat out, a transitory secretion results which only persists for about fifteen minutes after mastication is completed. *Hypnotic* suggestion that food is being taken produces similar slight effects. It is found, however, that gastric secretion may be readily *inhibited* from the higher centres. Thus when it was suggested to a hypnotized subject that he was falling out of an aeroplane, the secretion immediately ceased.

Appetite juice is not essential to health. It may be abolished by section of the vagi, and digestion is not impaired. The continuous secretion and the appetite juice are of value, however, in initiating the digestion of the food; the products of such digestion produce a further flow of gastric juice (p. 383).

Gastric Response to Food.—Pavlov showed that about half an hour after food enters the stomach, a further secretion of gastric juice occurs, presumably in response to the presence of the food. The cause of this second secretion is still undecided.

i. It persists after section of both vagi, so it is not due to a long reflex arc through the central nervous system.

ii. *Mechanical* stimulation of the gastric mucosa with straw, feather, sand, etc., is ineffectual. These stimuli are not "adequate," and may be violent enough reflexly to inhibit gastric secretion.

iii. Raw or coagulated egg albumin, boiled meat, carbohydrate, and fat introduced through an œsophagotomy opening into the stomach of a sleeping animal (so as to arouse no appetite juice) produce no secretion during the next two or three hours.

iv. *Water* and all forms of salt solution (iso-, hypo-, and hyper-tonic saline) excite a secretion of gastric juice in man and animals. Water is but a weak stimulant; if insufficient quantities are used (*e.g.* 150 c.cm. in dog) no response is obtained. In man the response varies in different individuals.

[Water introduced into the small intestine has a similar though slighter effect; water per rectum yields negative results. *Distension* of the rectum with water may produce reflex gastric secretion.]

v. *Meat extracts*, meat broth, or meat juice similarly given, are constant and active exciting agents. The nature of the potent chemical constituent is undetermined. Creatine, creatinine, proteoses, peptone, and the products of digestion of raw fibrin all give negative results.

The longer meat extracts are retained in the stomach, *e.g.* by mixing with starch paste to make a jelly, the more prolonged is the secretion which results.

vi. If the amount of secretion which results from sham feeding with bread and egg-white is compared with that obtained when these substances are swallowed and allowed to enter the stomach, it is found that the *psychic* secretion only constitutes half to one-third the *total* secretion. Some substance is produced during the process of digestion of these foods which further stimulates gastric secretion. If these semi-digested masses are introduced into the stomach of another dog, a much greater secretion of gastric juice results, than from an equivalent amount of undigested food and water. No secretagogue substance is produced during the digestion of starch.

vii. *Fat* taken during or after a meal of flesh *inhibits* both the psychic secretion and the response of the stomach to the presence of the food within it.

It is clear that water, an unknown constituent of meat juice, and some products of gastric digestion can produce a flow of gastric juice. Pavlov leaned to the view that these secretagogue substances acted by means of local nervous reflexes. A nervous plexus (Meissner) is found in the submucous coat of the stomach; some branches of the plexus lie between the epithelial cells and others pass to the gastric glands. It is possibly through this plexus that the "gastric response to food" is brought about. Chemical stimulation of any part of the mucous membrane will thus produce a secretory response from a wide area of the stomach; and one can readily understand why the reactions of the Pavlov pouch resemble so closely those of the large stomach.

"**Gastrin.**"—It has been suggested, however, that a substance called *gastrin* is formed in the pyloric mucosa under the influence of meat extracts, etc., that it is absorbed into the blood stream, passes to the fundus of the stomach and stimulates a further flow of gastric juice. It has been suggested that the "secretion" of gastrin accounts for the gastric response to food. In support of this view is the fact that extracts of pyloric mucous membrane made with 0·4 per cent. HCl, neutralized, and injected intravenously, produce a flow of gastric juice (Edkins), *i.e.* they contain a gastric secretagogue substance. It must be pointed out, however, that this merely shows that a secretagogue substance may be extracted from gastric mucosa, but does not prove that it is of any physiological significance. It has still to be shown that this secretagogue body (gastrin) actually enters the blood stream in the living animal, and promotes a flow of gastric juice; this has not been satisfactorily demonstrated.

(i) Active secretagogue substances with the same action as gastrin can be obtained from many tissues and substances—thyroid, liver, pancreas, bread, and meat; gastrin also stimulates pancreatic secretion; *i.e.* gastrin is specific neither in its origin nor in its site of action. It is well known that all tissue extracts contain histamine (p. 290), which has a powerful secretagogue action on the alimentary canal, particularly on the gastric glands (p. 387);

this may explain to a considerable extent the secretagogue action of extracts of stomach and other organs. "Gastrin" certainly produces vaso-dilatation, and its action is not abolished by atropine which paralyses the vagal terminals.

(ii) No gastric exciting substance is present in the blood leaving the stomach of fed animals.

(iii) Ivy and Whitlow prepared animals with two pouches: (i) a Pavlov pouch; (ii) a pouch of the entire pyloric antrum—which was divided from the fundus and the duodenum, closed at one end and the other brought to the surface; the continuity of the bowel was restored by means of a gastro-duodenostomy (see Fig. 99). In this experiment the nervous connections between the Pavlov and pyloric pouches were severed, but their blood supply was intact, so that any chemical substance which may have been liberated from the pyloric mucosa into the blood stream ought to have produced its customary effect. Various substances, such as food extracts, were introduced into the pyloric pouch, but *no* increased secretion occurred in the Pavlov pouch.

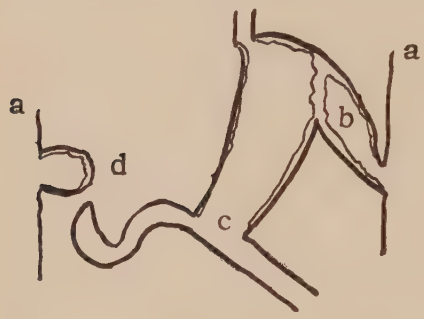

Fig. 99.

a=Abdominal wall; b=Pavlov pouch; c=gastro-duodenostomy; d=pyloric pouch. (After Ivy and Whitlow, *Amer. Journ. Physiol.*)

Gastrin is probably of *pharmacological* interest only, and it is highly doubtful whether it is formed or plays any part in the body normally (Carlson).

Other Factors in Gastric Secretion. — i. Acids, *e.g.* HCl, fatty acids, induce gastric secretion.

ii. Alkalis ($NaHCO_3$, $CaCO_3$) up to 1·5 grm. per kg. body-weight in two hours, *increase* gastric secretion in dogs with Pavlov pouches. If alkali is given in adequate doses in man and remains long enough in the stomach, its direct neutralizing effect more than counteracts its secretagogue action.

iii. *Distension of the stomach, e.g.* in pyloric obstruction in man, induces a very copious gastric secretion.

iv. Tea, coffee, and cocoa may contain a gastric secretagogue substance. *Condiments* act reflexly through the sense of taste. The vegetable *bitters* probably have no appreciable effect.

Gastric Secretion in Man.—The course of gastric secretion in man can be followed by means of the fractional test meal (p. 381). A careful distinction must always be drawn between gastric *contents* and pure gastric *juice*. The contents of the stomach consist of gastric juice, swallowed saliva, pancreatic and intestinal juices which have regurgitated through the pylorus, mucus secreted by the pyloric glands, and swallowed food in varying proportions.

1. Resting Contents.—After a night's fast, the stomach contains a varying amount of fluid, 30 c.cm. on the average; free HCl can usually be demonstrated (fasting secretion). The fluid consists of gastric juice, saliva, and mucus, and is often stained with bile which has regurgitated from the duodenum. If the stomach has been secreting rapidly and duodenal fluid

has not regurgitated, *e.g.* because of pyloric obstruction, the stomach contents may approach in composition that of pure gastric juice.

2. Ingestion of the pint of gruel usually lowers the free acid practically to zero level, owing to (i) dilution of the gastric juice ; (ii) its neutralization by swallowed saliva ; and (iii) its combination with the organic substances in the meal (Fig. 103).

3. The acidity then slowly rises, and after 1½ hours reaches 0·1 per cent. HCl (equivalent to 30 c.cm. $N/_{10}$ NaOH per 100 c.cm. of gastric contents) on the average. The presence of the food in the stomach has clearly called forth a second flow of gastric juice. As more of this juice is added to the stomach contents, the percentage of acidity slowly rises (Figs. 100, 103).

4. The further course of the curve depends largely on the behaviour of the pyloric sphincter; much light is thrown on the subject if the total chloride is estimated in addition to the total acidity. Bolton & Goodhart[1] have shown that the total Cl is the truest guide to the total amount of HCl secreted by the stomach ; the total Cl rises with varying degrees of rapidity and remains at its high level as the stomach empties (Fig. 100). The fall in the percentage HCl which is shown in the latter part of the curve is accompanied by a marked rise of inorganic Cl ; *i.e.* the acidity is falling probably because of *influx of alkali* from the duodenum (Bolton). Boldyreff showed that if acid solutions are introduced into the fasting stomach of the dog they are neutralized down to a fixed level of 0·15 to 0·20 per cent., and he proved that this was due to regurgitation of pancreatic juice from the duodenum. The mechanism of this regurgitation has been studied radiographically by Bolton and Salmond.[2] They find that from time to time *antiperistalsis* can be detected in the duodenum, which drives the food back into the duodenal cap (*i.e.* the first part of duodenum), which becomes distended ; whether any food enters the stomach or not depends on the state of the pylorus. During the early part of gastric digestion, the pylorus is contracted in the intervals between the gastric peristaltic waves ; during the latter part, however, it relaxes independently between the waves. Should the duodenal pressure then exceed the intragastric pressure, regurgitation takes place. The following variations in the behaviour of the pyloric region have been observed.

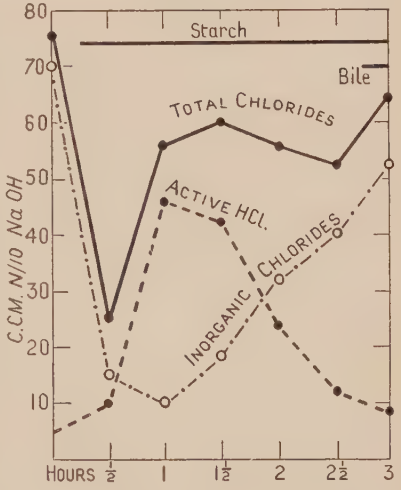

FIG. 100.—Normal curve of Total Chloride, Inorganic Chloride, and Active Hydrochloric Acid (Active HCl = free HCl + HCl combined with protein).—BOLTON.

[1] Bolton and Goodhart, *Lancet*, 1922, i. 420 ; Bolton, *Brit. Med. Journ.*, 1923, ii. 269.
[2] Bolton and Salmond, *Lancet*, 1927, i. 1230.

(i) Normally, pyloric relaxation and therefore alkali regurgitation into the stomach, begins during the second hour after the ingestion of the gruel and the curve of acidity steadily falls (Fig. 100).

(ii) The pylorus may fail to relax *between* the gastric peristaltic waves, regurgitation does not occur to any extent, and so the curve of acidity continues to rise, running parallel to that of total Cl—"*climbing type*" of curve (Figs. 101, 103 A). Such stomachs may empty quite quickly, but the consequent rapid rush of food through the duodenum is unfavourable to regurgitation.

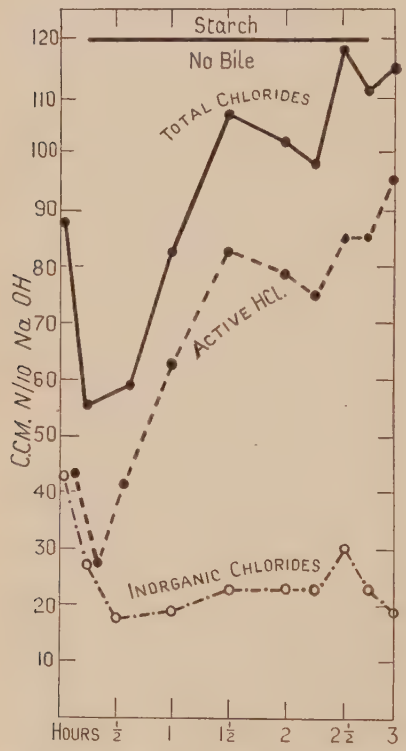

FIG. 101.—Duodenal Ulcer with little Alkaline Regurgitation into Stomach. "Climbing" type of curve (so-called "hyperchlorhydria"). —BOLTON.

(iii) Relaxation of the pylorus between gastric peristaltic waves may occur almost from the beginning of digestion, giving rise to the presence of bile in the stomach and a very low percentage or complete absence of free HCl in the stomach (Fig. 102). Such stomachs are usually found to be atonic.

The acidity of the gastric contents depends (i) on the *behaviour of the pylorus*, as discussed above, (ii) on the *amount of gastric juice secreted*. The terms *hyperchlorhydria* and *hypochlorhydria* simply mean that the acidity of the gastric *contents* is greater or less than normal. The former may be due to excessive secretion or deficient regurgitation, and the latter to diminished secretion or excessive neutralization. The total acidity usually exceeds the free HCl by about 10 c.cm. $N/_{10}$ NaOH per cent.

In 5 per cent. of normal subjects in perfect health and with no symptoms of indigestion, no HCl whatever is secreted. The condition is called *achylia gastrica* (Fig. 103 B). It may be congenital in origin and due to non-development of the oxyntic cells. The antiseptic action of HCl in the stomach is thus lost; it is suggested that such subjects may become liable to infection with organisms which pass into the duodenum and flourish there. Achylia is a constant accompaniment of *pernicious anæmia* (p. 204).

In *cancer* of the stomach, free HCl is often absent from the gastric contents. This is probably due to the inflamed condition of the mucosa. If the interior of the stomach is washed to remove adherent mucus, evidence of gastric secration can usually be obtained (Bennett).

Pure Gastric Juice can be obtained in animals from a Pavlov pouch. In man, the fasting stomach contents in cases with very rapid secretion approximate to pure gastric juice as the neutralizing effect of duodenal regurgitation is reduced to a minimum. Subcutaneous injection of *histamine* produces a profuse flow of gastric juice which can be used for analysis.

The *composition* is very similar in man and the dog, *i.e.*:

1. Free HCl, 0·4 to 0·5 per cent. (*i.e.* about $N/_{10}$ HCl). Total acidity, 0·43 to 0·6 per cent.

HCl is produced by half-moon-shaped cells, staining pink with eosin (*parietal* or *oxyntic* cells), which are only found in the cardiac part[1] of the stomach, and lie external to the chief or peptic cells. The exact mode of formation of the acid is unknown. It is possible that NaCl interacts with some weak acid, *e.g.* H_2CO_3, to form HCl, which is at once eliminated from the cell into the lumen of the duct (cf. Hamburger phenomenon). The stomach usually secretes juice of a *constant* acidity; possibly when it is secreting rapidly it may form juice of a higher degree of acidity.[2]

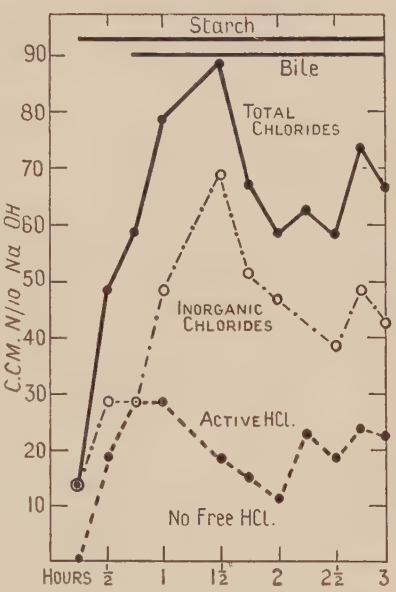

Fig. 102.—Functional Disorder. Excessive Neutralization.—Bolton.

No free HCl present, the active HCl being all acid combined with protein. The curve of total chlorides proves that considerable secretion has taken place, but the acid was almost completely neutralized by regurgitation of alkali from intestine.

2. Proteolytic ferment—*pepsin*—which is activated by the presence of HCl and breaks protein down to peptones (p. 433).

3. The presence of a special milk-curdling ferment—*rennin*—which converts soluble caseinogen in the presence of calcium into insoluble calcium caseinate, is disputed (p. 433).

4. *Mucin* secreted by the pyloric glands.

5. *Bacteria*, 25 to 100,000 organisms per c.cm., chiefly *Bacillus coli*, staphylococci, and non-hæmolytic streptococci. The importance of the bactericidal power of gastric juice is usually overestimated, but it probably prevents virulent organisms, *e.g.* hæmolytic streptococci, from entering the duodenum alive.

Secretion of Pancreatic Juice.—Methods.—The portion of the duodenal wall which receives the pancreatic duct is exsected and brought out on to the surface. The continuity of the bowel is restored. The juice is collected by means of a cannula which is inserted into the duct.

[1] " Cardiac " is used in the sense defined on p. 403.

[2] MacLean (*Journ. Physiol.*, 1928, vol. lxv. p. 77) admits that the juice secreted has a constant chloride content, but claims that the juice which is formed during the latter phases of gastric secretion contains *less free HCl* and *more neutral Cl* than that formed earlier.

Pancreatic secretion begins 1½ minutes after the beginning of a meal. It increases rapidly when food enters the duodenum and continues for 2 or 3 hours. It is probably controlled by the vagus and by a chemical mechanism—secretin.

Rôle of Vagus.—Using the experimental technique described on p. 381, Pavlov demonstrated that stimulation of the peripheral end of the cut vagus results in a secretion of pancreatic juice. There may be a long latent period,

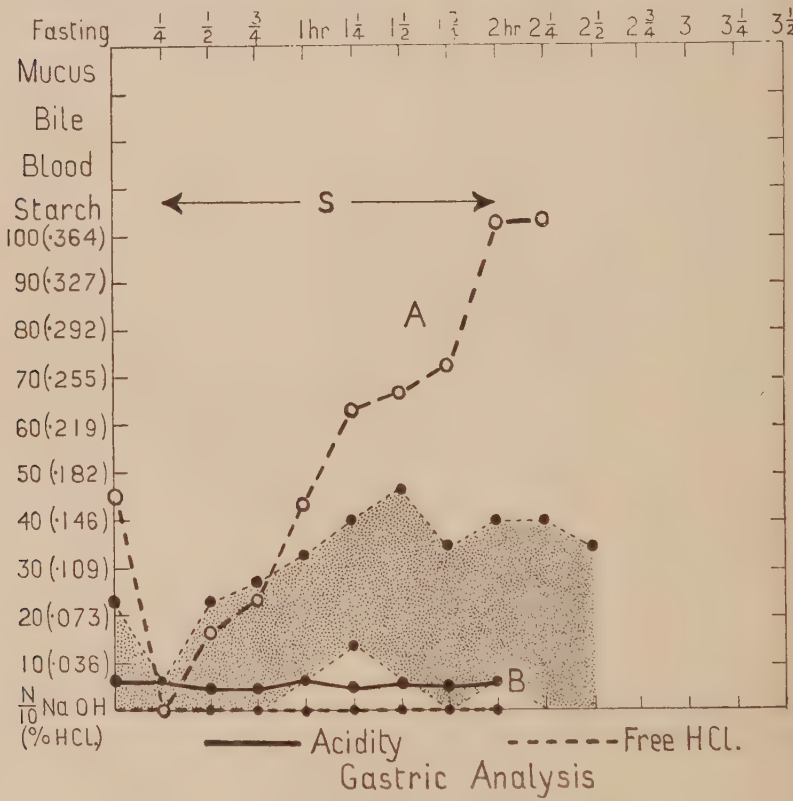

FIG. 103.—Gastric Analysis.

Shaded area represents the limits of free HCl in 80 per cent. of healthy males after a test meal. A = "Climbing" type of curve; B = Achylia gastrica; S = Emptying time of stomach as measured by presence of starch.—BENNETT and RYLE.

up to half an hour, which is perhaps due to simultaneous constriction of the pancreatic ducts. Until the vagal fibres to the ducts are fatigued, no juice can escape (Babkin). The *initial* flow of pancreatic juice in the intact animal may be due to a vagal reflex. Stimulation of the vagus results in shrinkage of the cells of the pancreas and disappearance of the contained granules, indicating that secretory activity is occurring. The juice which is formed is viscid and rich in ferments.

Secretin.—It is suggested that a chemical substance—"*secretin*"—is

present normally in the mucous membrane of the upper intestine and that under certain conditions it enters the blood stream and stimulates the pancreas to secretory activity. The older evidence may be summarized as follows :

1. The introduction of acid into the duodenum, the upper intestine, and to a less extent the lower intestine, produces a flow of pancreatic juice.

2. If the mucous membrane of the duodenum or jejunum is scraped off, rubbed with sand and 0·4 per cent. HCl, filtered, neutralized, and injected intravenously, a marked fall of blood pressure occurs which is followed after 20 seconds by an increased flow of pancreatic juice (Bayliss and Starling). It was suggested that acid in the duodenum, or the artificial treatment of the duodenal mucosa with acid, acts on a substance present in the epithelial cells, which was named " prosecretin." This is converted into *secretin*, a soluble hormone which passes into the blood stream to the pancreas, and stimulates it to greater secretory activity. A preparation of secretin was prepared, with no depressor action, but with potent secretagogue activity.

3. The crucial experiment to prove the rôle of secretin in the body was as follows. The spinal cord and solar ganglia in the abdomen were destroyed. A loop of jejunum was isolated and its nerve supply destroyed without interfering with the blood supply. The injection of acid into this denervated loop caused a flow of pancreatic juice. As all nervous connections between the loop and the pancreas were probably severed, the acid could only have acted by liberating some chemical substance (secretin) which passed in the blood stream to reach the pancreas (Bayliss and Starling)

It must be pointed out, however, that in patients with achylia gastrica (p. 386) or after complete gastrectomy, though no HCl enters the duodenum, pancreatic secretion occurs normally, as shown by the characteristic fall in alveolar CO_2, two hours after a meal (p. 225 and Fig. 64).

The injection of secretin produces very slight histological changes in the pancreatic cells. The juice formed is thin, watery, strongly alkaline, contains much inorganic matter, but is poor in ferments. After repeated injection of secretin the pancreas finally fails to secrete. Stimulation of the vagus will then still elicit a copious flow of active juice (Mellanby).

The above considerations suggest that the rôle of the vagus is very important, and that it is chiefly responsible for the secretion of the enzymes of pancreatic juice ; secretin may perhaps be responsible for the secretion of water and alkali by the pancreas.

Mellanby has shown recently that secretin can be extracted from intestinal mucosa by means of water, 0·05 per cent. NaOH, and absolute alcohol. These findings suggest that secretin exists *as such* in the mucosa and not in the form of a precursor. In the cat secretin is limited to the duodenum, in the pig it is found up to 10 feet from the pylorus. If a solution of bile salts is added to an acid extract of duodenal mucosa, the bile salts are precipitated together with the secretin which is *adsorbed* on to them. The secretin can then be extracted with water and is obtained in a purified form, which does not lower the blood pressure on intravenous injection, and which gives the chemical reactions of a *polypeptide*. According to Mellanby the introduction of *acid bile* into the duodenum is a very potent method of eliciting a flow of pancreatic juice. The *p*H of the bile needed depends on the state of the animal : within 4 hours of feeding *p*H 6·5, after 24 hours starvation, *p*H 8·0 are required. The acid reaction usually necessary may explain why the older

workers found that acid introduced into the duodenum (which possibly already contained bile) aroused pancreatic secretion. Sodium cholate at the right reaction produces the same results, so that it is apparently the effective constituent of bile. The bile salts themselves, on intravenous injection, are *not* secretagogue to the pancreas, so it must be assumed that when they are themselves absorbed (p. 392) they carry secretin into the portal blood. The mucin present in bile slows down the rate of absorption of the bile salts and thus gives a prolonged flow of pancreatic juice.

According to Pavlov the ingestion of *fat* gives rise to a flow of pancreatic juice which is rich in lipase. *Water* too is said to excite pancreatic secretion. *Alkaline* solutions exert an inhibitory effect.

Composition.—Pancreatic juice contains the following constituents :

1. Na_2CO_3 in such concentration that pancreatic juice neutralizes approximately equal amounts of gastric juice.

2. *Trypsin*—a powerful proteolytic ferment which breaks down proteins to polypeptides and liberates certain amino-acids, *e.g.* leucine, tyrosine. Juice collected from the pancreatic duct is inactive, and is said to contain a precursor called *trypsinogen*. It is activated by a constituent of the succus entericus called *enterokinase*, which is believed to be a proteolytic ferment acting best in a neutral medium. Trypsinogen contains a protein moiety which masks its proteolytic action. The activation of trypsinogen depends on dissolving off this protein which is combined with it. The presence of calcium salts facilitates this process.

3. *Amylase*—converts all forms of starch rapidly into maltose.

4. *Lipase*—splits fats to glycerine and fatty acids (p. 426).

If the pancreatic duct is ligatured in animals, 60 to 80 per cent. of the ingested fat is lost in the fæces, owing to non-digestion of the fats from the absence of lipase ; absence of both pancreatic juice and bile results in the loss of 80 to 90 per cent. of the ingested fat.

In pancreatic disease variable results are obtained owing to differences in the degree of failure of the external secretion. A natural emulsion like milk is better digested than an unemulsified or artificially emulsified fat ; this observation suggests that the gastric and intestinal lipase may bring about considerable splitting of fat. When fatty stools are encountered, they may contain 20 to 90 per cent. of neutral fat. The fæces in pancreatic deficiency also contain incompletely digested meat fibres, which still possess unbroken nuclei. The loss of the pancreatic juice results in ill-health or death from inanition, unless the diet is carefully selected and contains much carbohydrate and predigested proteins.

Secretion of Succus Entericus.—To investigate the factors controlling the secretion of succus entericus a loop of intestine is separated and both free ends are sutured into the abdominal wall ; the continuity of the bowel is restored. The secretion of the loop can be collected and studied.

1. A flow of intestinal juice follows a meal. It is slight during the first two hours, but shows a marked increase in the third hour. It is most marked in the upper end of the gut.

2. According to Pavlov the presence of pancreatic juice in the intestine is the most effective stimulus to the flow of succus entericus.

3. It is claimed that intravenous injection of secretin or of intestinal juice may produce a flow of succus entericus.

4. *Mechanical* stimulation of the intestinal mucous membrane produces secretion, possibly through a local nervous reflex. This juice, however, is said to contain little or no enterokinase which is only secreted under the influence of pancreatic juice, *i.e.* pancreatic juice is responsible for the secretion of the ferment which activates its constituent—trypsinogen.

Composition.—Succus entericus is an alkaline fluid containing ferments which complete the breakdown of the food-stuffs.

1. *Erepsin* can break down caseinogen slowly; but it acts rapidly on peptones and polypeptides, converting them into amino-acids.

2. *Invertase* converts cane sugar into glucose and lœvulose; *maltase* breaks down maltose to two molecules of glucose; *lactase* converts lactose into glucose and galactose.

It is possible that these ferments are present in an active form in the mucous membrane and exert their main digestive action in the wall of the bowel, and not in the lumen of the intestine.

3. *Enterokinase* activates trypsinogen (p. 390).

4. *Lipase* (see p. 426).

Almost complete absorption of the products of digestion occurs in the small intestine.

Large Intestine.—The large intestine *secretes* mucus which allows the easy passage of the fæces. It *excretes* the heavy metals, *e.g.* iron, bismuth, mercury. The amount of calcium excreted in the fæces depends on several factors. If there is much phosphate in the diet, it is eliminated in combination with it. In man, 95 per cent. of the calcium is eliminated in the fæces and 5 per cent. in the urine. *Absorption* of water, salt, and glucose can occur in the large intestine (see p. 407).

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Bayliss and Starling.—*Journ. Physiol.*, 1902, vol. xxviii. p. 325.

The Bile.—Bile can be collected from the common bile duct or from the gall-bladder. In the latter case, it is considerably more *concentrated* and in addition contains *mucin* which is secreted by the gall-bladder epithelium.

Bile is an alkaline fluid containing inorganic salts and Na_2CO_3. The principal organic constituents of bile are as follows: 1. Bile pigments; 2. Bile salts; 3. Lipoids (cholesterol and lecithine); 4. Mucin. The origin and significance of each will be discussed.

1. The Bile Pigments are *bilirubin* and *biliverdin*. We noted (p. 201) that bilirubin is formed in the reticulo-endothelial system, from the hæmoglobin of destroyed red blood cells. It circulates in the blood stream and is excreted by the liver cells from the vascular capillaries into the bile channels. Biliverdin is an oxidation product of bilirubin which is formed in the bile passages. The bile pigments are mere waste products and serve no digestive

purpose. Their excretion in the fæces and urine and their possible resynthesis in the liver into a more complex body were discussed on p. 204.

2. The Bile Salts consist of sodium glycocholate and sodium taurocholate. *Cholalic* acid is a substance whose origin and structure are so far unknown. It contains no nitrogen, and may be a hexa hydro-benzene (Whipple), and is structurally related to turpentine and camphor. It is alleged (on scanty evidence) to be formed from cholesterol by the Kupffer cells of the liver. The bile salts help to keep the cholesterol of the bile in solution (see p. 396).

Glycine (of glycocholic acid) is amino-acetic acid and is readily formed in the body. *Taurine* $CH_2NH_2.CH_2SO_2.OH$ (of taurocholic acid) is a sulphur-containing body which may be derived from the cystine of the food or of the body proteins. There are about equal amounts of the taurocholate and the glycocholate in human bile. In the dog and sheep it is mainly the glycocholate which is present. If taurine is injected intravenously and cholalic acid given by the mouth, they are united in the body and the bile-salt excretion is increased. There is no direct evidence as to where the bile salts are normally formed. If the liver epithelium is injured by small doses of poison, or if its blood supply is diminished by an Eck's fistula, the excretion of bile salts is greatly lessened. During fasting, the supply of taurine is limited and this lowers the bile-salt excretion to a minimum. On a full diet the limited supply of cholalic acid controls the amount of bile salt formed.

Influence of Diet.—(i) During fasting there is a uniform minimal excretion of bile-salts; (ii) High protein feeding raises the bile-salt excretion to a maximum. (iii) Feeding with sugar lowers it.

On a normal diet there are great variations day by day depending probably on the amount of meat and starch in the food.

Rôle in Intestine.—The bile salts facilitate the digestive action of all the pancreatic enzymes—lipase (p. 426), amylase (p. 415), and trypsin (p. 433). They greatly aid the absorption of the products of fat digestion. When the common bile duct is *obstructed*, 25 to 75 per cent. of the fat intake is lost in the fæces, mainly in the form of fatty acids and soaps, showing that absorption has been very imperfect owing to absence of the bile salts. There is also an increase in the absolute amount of neutral fat excreted (*e.g.* 7 grm. compared with the normal of 1·7 grm.) so that digestion is defective too.

Circulation of Bile Salts.—The bile salts are reabsorbed from the intestine, are carried back to the liver, and are then re-excreted in the bile. The evidence is as follows:

(1) No bile salts appear in the fæces, though a trace of a decomposition product of cholalic acid–dyslysin is found.

(2) If the bile duct is brought up to the surface in a dog and the bile collected, it is found, as stated above, that during fasting there is a uniform minimal excretion of bile salts, proving they are formed constantly in the body. If bile salts are then given by the mouth they are *quantitatively* eliminated from the fistula in six hours.

According to Mellanby the bile salts during absorption carry the secretin which is present in the duodenal mucous membrane into the portal circulation and thus promote the flow of pancreatic juice (p. 389). When the bile salts reach the liver they stimulate it to secrete more bile (p. 394).

If bile salts are regularly formed in the body and are always returned to

the liver for re-excretion, the amount in the bile would rise to an enormous figure—the animal would be "turned into a pillar of bile salts" (Whipple). Clearly there must be some method of controlling the production and destruction of bile salts, but the nature of the process is so far unknown.

3. **Cholesterol.**—The main facts about the metabolism of cholesterol will be summarized here:

Sources.—The chief sources of cholesterol in the food are yolk of eggs, brain, fats, cream, butter, fat bacon, pork, liver, and kidney.

Distribution.—It is widely distributed in most of the cells of the body, and is usually found together with *lecithine*. It is probably a constituent of all cell membranes; it is found in the red cells and large amounts are present in the ovaries, the suprarenal cortex, and the white matter of the nervous system, especially the brain. Most of the cholesterol derived from cellular disintegration is retained and is not eliminated.

Effects of Ingestion.—Cholesterol taken in the food is largely absorbed into the blood. Some is excreted into the bile. A proportion of this is allowed to escape in the fæces after being reduced by intestinal bacteria to *coprosterol*. The rest of the cholesterol is reabsorbed into the blood once more, together with the bile salts. It may be sent to the tissues to repair tissue waste. It is difficult to see why cholesterol should be eliminated in the bile if it is going to be reabsorbed to a large extent.

The cholesterol of the bile can perhaps be regarded as an excretion from the blood, for in general the percentage in the bile varies with that in the blood. A lipoid-free diet may be associated with a low bile cholesterol. Excess feeding with cholesterol produces slight changes in the amount of cholesterol in the bile.

Synthesis.—There is some evidence that cholesterol can be synthesized in the body. On some diets the output may be greater than the intake.

Vitamins.—It is believed that vitamin A and the anti-rachitic vitamin (D) are closely related chemically to cholesterol. Under the influence of ultra-violet rays *ergosterol* (which is found in minute amounts in unpurified cholesterol) can be converted into a potent anti-rachitic body (p. 449).

Blood Cholesterol.—The normal level is between 0·15 to 0·2 per cent. It is equally distributed between the plasma and the corpuscles.

After a large meal of *fat* there may be a slight rise in the blood cholesterol, depending on the amount of cholesterol which has been ingested (cf. p. 428). In any condition of "*lipæmia*," *i.e.* one in which much fat is being transported in the blood, as in diabetes or starvation (when the fat depôts are called upon), some increase in the blood cholesterol (and lecithine) may occur.

Pregnancy.—A considerable retention of cholesterol occurs in the blood during the last three or four months of *pregnancy* (up to 0·25 to 0·45 per cent.); the increase persists for a short time after parturition and the excess is got rid of by excretion in the milk, probably to increase the low cholesterol content of the child's blood. The suprarenal cortex becomes laden with cholesterol during pregnancy, but the bile cholesterol is low. After parturition, however, it rises to two or three times its normal level, and crystals of cholesterol may be deposited in the bile passages.

Menstruation.—There is said to be a premenstrual rise in the blood cholesterol.

Adrenal Cortex.—(See p. 126).

Blood Diseases.—Cholesterol inhibits hæmolysis of red cells *in vitro* and *vivo*. After splenectomy for acholuric jaundice the blood cholesterol is said to rise. It is lowered in all forms of chronic anæmia. Cholesterol may be related to the *defence* mechanisms of the body. The blood cholesterol is low during acute infectious diseases and tends to rise as recovery occurs.

In so-called "*lipoid nephrosis*" (p. 307) with extensive œdema, the blood cholesterol is raised even to 1·2 per cent. In *diabetes*, as mentioned, the rise in blood cholesterol runs parallel to the severity of the case, and is an indication of the extent to which fat is being called upon for energy purposes. A patient with *gall-stones* who is not jaundiced shows no alteration in the blood cholesterol, so no help in diagnosis can be obtained from such determinations. *Jaundice* of the chronic obstructive type from any cause is associated with a high blood cholesterol (0·25 to 0·7 per cent.), because the constituents of the bile are passed back into the blood.

It is stated that rabbits fed on cholesterol-rich diets show changes in the internal coat of the arteries.

The Secretion of Bile.—It can be shown in an animal (or man) with a fistulous opening into the gall-bladder and the common bile duct tied, that the secretion of bile by the liver is a continuous process. About the third hour after the ingestion of food there is an increase in the amount of bile formed; there is a slight decrease in the flow at night. The injection of secretin or stimulation of the vagus nerve has a minimal effect on bile secretion (Whipple). The most powerful *cholagogue* is whole bile or its active principle, the bile acids. If 8 to 12 grm. taurocholic acid are ingested, there is an increase in the bile flow lasting 24 to 48 hours, and the ingested acid can be recovered quantitatively from the bile. Glycocholic acid acts less powerfully; salicylates have a variable effect.

Experimental procedures, *e.g.* pulling on the gastro-hepatic omentum, opening and closing the abdomen, the administration of an anæsthetic, temporarily inhibit the flow of bile.

The total amount of bile formed in man is 500 to 1000 c.cm. in twenty-four hours. Bile is secreted at a low pressure (about 300 mm. bile), and so its flow can be readily obstructed. Life and health cannot be maintained for more than a few months in the *complete* absence of bile from the intestine. If 10 to 20 per cent. of the total bile formed reaches the duodenum, normal health and functional activity are preserved (dog).

Functions of the Gall-Bladder.[1]—The gall bladder is a thin-walled structure, which in man can hold about 50 c.cm. of bile. This is 6 to 10 times as concentrated as the bile in the hepatic ducts owing to the absorption of water by the mucous membrane. The valves of Heister [spiral valve] at the junction of the gall-bladder and the cystic duct do not resist to any appreciable extent the flow of bile in or out of the gall-bladder. The wall of the gall-bladder normally shows slow, small, irregular contractions, which are readily inhibited by operative procedures; *adrenaline* produces powerful contraction of the gall-bladder, but stimulation of the vagus has little or no effect (Boyden). The common bile duct runs obliquely through the wall of the duodenum, so that when this part of the bowel is contracted it closes the duct. Just before the duct pierces the duodenum it is surrounded by additional muscle fibres called the *sphincter of Oddi*.

[1] Whitaker, *Amer. Journ. Physiol.*, 1926, lxxviii. 411.

The movements of the gall-bladder in animals are best studied as follows : the gall-bladder is opened, emptied of bile, and filled with iodized oil which is opaque to the X-rays. If no food is given for 24 hours the oil remains in the gall-bladder, which can then be examined radiographically (Whitaker). It is found that the most effective stimulus to contraction is the presence of large amounts of *fat* in the intestine, particularly egg yolk, and to a less extent protein. Expulsion of the oil from the gall-bladder begins in 5 to 30 minutes, and continues regularly or intermittently until the organ is emptied after 2 to 5 hours. The same results are obtained after tying the lacteals or division of the vagi and of the sympathetic nerves to the gall-bladder, suggesting that some substance enters the blood stream from the bowel and causes contraction of the gall-bladder. The injection of secretin, or the introduction of HCl into the duodenum, is without effect ; bile salts actually produce an *increase* in the size of the gall-bladder shadow, probably owing to increased secretion of bile by the liver. If the egg yolk is hurried through the intestine and not absorbed, emptying of the gall-bladder does not occur. Boyden suggests that the products of fat digestion (and to a less extent of protein digestion), after absorption, stimulate the gall-bladder. It has been supposed that as each wave of peristalsis in the duodenum is preceded by a wave of relaxation, the alternate relaxation and contraction of the muscle round the termination of the common bile duct might " milk " the bile into the bowel. This is not the case however, for active peristalsis may take place in the intestine (after a barium meal or the injection of physostigmine) without the gall-bladder being emptied. Respiratory movements are unimportant because all the intra-abdominal structures are uniformly compressed. We may conclude that the presence of certain foods in the bowel increases the secretory activity of the liver and causes partial or complete emptying of the gall-bladder, bile thus being provided to assist the digestive processes. Except in response to the presence of large amounts of fat in the bowel, the gall-bladder does not usually empty itself completely, but fills slowly and empties irregularly ; this is shown by the fact that on a normal mixed diet, dye-stuffs introduced into the gall-bladder are still found there after one to three days, but not after seven days.

During a *fasting* period the tone of the sphincter of Oddi rises so that it can resist a pressure of about 300 mm. bile. The liver continues to secrete, and when the pressure in the bile ducts exceeds 70 mm. bile, bile begins to flow into the gall-bladder, where it is stored until it is needed during the next meal. Although the gall-bladder can only hold a small quantity of *fluid*, it can store the *solid* matter of a large amount of liver bile, because 50 c.cm. of bladder bile represent the content of solids of 300–500 c.cm. of liver bile. In this way the gall-bladder acts as a very effective reservoir in spite of its small volume, and it prevents the pressure in the bile passages from rising excessively. After removal of the gall-bladder in man, the bile ducts become dilated to accommodate to some extent the bile which is continuously secreted by the liver ; if the tone of the sphincter of Oddi is high, the pressure in the biliary passages rises until it may equal or exceed the secretory pressure of the liver cells and thus interfere with their activity. If the tone of the sphincter is low (as it often is for a time after cholecystectomy), bile dribbles into the intestine when it is not needed and is consequently wasted. During *periods of digestion* the sphincter of Oddi yields at a pressure of about

100 mm. bile ; this relaxation of the sphincter and the contraction of the gall-bladder result in the discharge of bile into the intestine. The importance of the reservoir action of the gall is illustrated by the following experiment. If the common bile duct is tied and the gall-bladder removed, jaundice appears in 3 to 6 hours ; but if the gall-bladder is left it can store so much bile pigment that jaundice does not develop for 36 to 48 hours.

It is claimed by Meltzer that certain salts cause relaxation of the sphincter of Oddi and tonic contraction of the gall-bladder. Lyon has made use of this observation : a tube is passed into the duodenum, a 33 per cent. solution of *magnesium sulphate* is introduced, and the bile is collected at intervals. The first samples are light yellow, and come from the common bile duct ; then follows darker and more viscid bile from the gall-bladder ; and, finally, light thin bile is obtained from the hepatic ducts, which is of low specific gravity, and contains only traces of cholesterol. This technique can be employed to drain the biliary passage or to collect bile for bacteriological and microscopical investigation.

It must be pointed out, however, that magnesium sulphate given by mouth is probably equally effective ; that, studied radiologically, the Lyon technique does *not* cause powerful contraction of the gall-bladder ; and that it seems more reasonable to give fat which is known to empty the gall-bladder.

Removal of the gall-bladder has little effect on gastric secretion. The mucous membrane of the gall-bladder excretes certain substances which reach it by way of the blood stream ; it thus removes bacteria from the blood and may itself be damaged in the process.

Cholecystography.—A radiographic method of studying the biliary system in man has been introduced by Graham. Tetra-iodo- and tetrabrom-phenolphthalein are excreted by the liver from the blood, and pass into the gall-bladder, where the dye is concentrated by absorption of water, and becomes opaque to the X-rays. The size, shape, and behaviour of the gall-bladder can be studied radiographically. The dye which is present in the liver and the bile ducts is too dilute to cast a shadow. It is safer to administer the dye by the mouth in formalized gelatin capsules ; when given intravenously, toxic symptoms may be produced ; given subcutaneously local necrosis results. Fat and, to a less extent, protein causes rapid emptying of the gall-bladder in 3 to 8 hours (cf. p. 395).

Cholecystography is employed in the diagnosis of gall-bladder disease. If one can be sure that the dye-stuff has been absorbed from the bowel and yet *no* shadow of the gall-bladder is obtained, it shows that either the cystic duct is obstructed or the gall-bladder is sclerosed, or else that the gall-bladder wall is unhealthy so that the normal concentration of the contents is not brought about.

Gall-Stones.—1. Pure *cholesterol* gall-stones are due to a disorder of metabolism. As a result of high cholesterol excretion in the bile, associated perhaps with diminished formation of bile salts (which keep cholesterol in solution), precipitation occurs. If rabbits (which normally have no cholesterol in the bile) are fed with diets rich in cholesterol it is found that cholesterol is excreted into the bile ducts and intrahepatic stones are formed. If secondary infection occurs, an exudate rich in calcium is poured out ; in addition, the emptying of the gall-bladder is interfered with as a result of the inflammation which is present. A mass of calcium, organisms, shed epithelial cells,

leucocytes, and more cholesterol is then deposited on top of the original pure cholesterol stone.

2. Pure *pigment* stones may be present. They are always multiple and are found in large numbers in the gall-bladders and ducts. They vary in size from a grain of rice to a pea and consist of bilirubin and calcium. Their causation is unknown.

3. Infection and Stasis.—*Inflammation* of the gall-bladder and biliary *stasis* can lead to the formation of gall-stones. Organisms may enter the blood stream from a septic focus, *e.g.* appendix, teeth, tonsils, and be excreted by the liver into the bile passages and so reach the gall-bladder, or be directly excreted by the gall-bladder epithelium. Inflammatory exudate is formed, and the bile is altered in consistency and character, leading to the formation of mixed stones containing cholesterol, pigment, calcium, organisms, etc.

Functions of the Liver.—The functions of the liver are discussed in various sections of this book, and reference to them will be given here :

1. Bile formation, p. 394 ; 2. Destruction of red cells and jaundice, p. 201 ; 3. Protein metabolism, p. 433 ; 4. Fat metabolism, p. 430 ; 5. Carbohydrate metabolism, p. 447 ; 6. Antitoxic and protective function, p. 400 ; 7. Coagulation of blood, p. 400 ; 8. Formation of fibrinogen, p. 400.[1]

Extirpation of the Liver.—Mann and Magath have recently succeeded in completely extirpating the liver in the dog by means of a three-stage operation : (i) Lateral anastomosis of the portal vein to the inferior vena cava and ligation of the latter on the headward side of the stoma. All the blood from the posterior part of the body has to pass through the liver, but as the capillaries in that organ offer a considerable resistance, a collateral circulation is established through the azygos and internal mammary veins. (ii) Ligature of the portal vein at its entrance to the liver. All the blood must now flow through the collateral circulation. (iii) Removal of the entire liver and the portion of the inferior vena between the first ligature and the diaphragm. These researches have thrown a flood of light on many aspects of liver function.

The animal recovers rapidly from the anæsthetic, and remains apparently normal for 3 to 8 hours. The following symptoms then develop coincidentally with a progressive and invariable *decrease of the blood sugar* which may fall to 0·04 per cent. : (i) Muscular weakness—the animal is unable to move any muscle except those of respiration ; there is loss of all reflexes and complete flaccidity ; (ii) after a short period there is a sudden return of the reflexes which are now exaggerated ; twitchings, general convulsions, vomiting, occur, and death takes place 2 hours after the first onset of symptoms.

1. Carbohydrate Metabolism.—The fall of blood sugar runs parallel with the aggravation of the clinical condition. The administration of glucose in doses of 0·25 grm. to 0·5 grm. per kg. body weight to a flaccid and comatose animal produces astonishing effects : within 30 seconds the animal can walk and respond to a call. The *heart* beats more strongly and becomes regular. The blood sugar following the injection reaches a high level ; when it decreases again symptoms reappear. Maltose and mannose act somewhat like glucose, but more slowly—recovery is gradual and not so long lasting ; presumably they are converted into glucose in the blood. It is somewhat remarkable that lævulose and lactose are quite ineffective ; dextrin and galactose have a slight action, but they may act in virtue of the glucose they contain as an

[1] Liver treatment of anæmia, see pp. 196, 205 ; structure of liver, see p. 199.

impurity. Glycogen given intravenously gives striking relief in a few minutes. If the blood sugar is kept normal by the continuous infusion of glucose the animal may survive 18 to 24 hours. Finally, however, restlessness, dyspnœa, and vomiting occur; the animal becomes ataxic, and does not appear to hear or see. Coma and anuria develop, and death takes place quite suddenly. These terminal symptoms are unrelieved by glucose. The first group of symptoms described on p. 397 were undoubtedly due to hypoglycæmia; the cause of these terminal manifestations is unknown.

It is obvious from these results that the liver plays an important part in regulating the normal blood sugar level. It is not only a storehouse of glycogen, but also *elaborates* sugar from some other foodstuff (p. 420). The liver glycogen may be exhausted as a result of starvation, but the blood sugar remains at its normal level till the end, although sugar is continually being withdrawn from the blood to supply the needs of the tissues; but if the liver is removed, as previously shown, hypoglycæmia rapidly develops. The study of the diabetic animal shows that the liver elaborates sugar principally from protein (p. 420).

Muscle Glycogen.—The total glycogen content of all the muscles is, normally, about as great as that of the liver. After hepatectomy the muscle glycogen decreases, *e.g.* from 0·8 per cent. to 0·4 or even 0·1 per cent. There is a relationship between the muscle glycogen content previous to the operation and the time of onset of symptoms: if the initial muscle glycogen content is high there may be no symptoms for 10 hours; if low, symptoms may be present in 2 hours. If glucose is given to dehepatized animals in amounts sufficient to produce hyperglycæmia, glycogen is re-formed in the muscles. It appears, however, that the muscle glycogen is not as readily available as liver glycogen for the *blood stream*; for fatal hypoglycæmia may occur with enough muscle glycogen to maintain the normal level of the blood sugar for a considerable period.

Adrenaline and *asphyxia*, which normally raise the blood sugar (p. 417), fail to do so after hepatectomy, proving that they act directly on the liver.

Relation of Liver to Pancreatic Diabetes and to Insulin.—(*a*) If the liver and pancreas are removed simultaneously, liver symptoms alone are present. Hypoglycæmia develops in a typical manner; it is relieved by glucose, and death occurs a little earlier than is usually the case.

(*b*) If pancreatectomy alone is carried out, after 24–48 hours the blood sugar is two to four times the normal. If hepatectomy is now performed, there is an immediate fall in the blood sugar, symptoms develop more rapidly and *at a higher level of blood sugar than usual*. The animal can be restored by glucose, but dies in a few hours.

(*c*) If hepatectomy is carried out 48–96 hours after pancreatectomy (when the blood sugar is four to five times the normal), characteristic symptoms of liver extirpation develop with a blood sugar level *above normal* (*i.e.* above 0·1 per cent.). Glucose has a fleeting restorative action, and death rapidly occurs in coma.

It is important to note that once the central nervous system has become adapted to a high level of blood sugar, a rapid decrease in the blood sugar produces hypoglycæmic symptoms, although non-diabetic animals would not show symptoms at such levels. (Cf. insulin in diabetes, p. 423.)

The above experiments prove that the hyperglycæmia of diabetes is

dependent on the liver. As the fasting diabetic with exhausted liver glycogen also shows a pronounced hyperglycæmia, it appears the *blood sugar of the diabetic is largely made in the liver* (from protein) (cf. p. 420). Owing to loss of the controlling influence of insulin, the liver in the diabetic is elaborating sugar extravagantly and without regard to the needs of the body (cf. p. 424).

The injection of *insulin* after hepatectomy causes a fall in the blood sugar level, proving that the liver is not essential for its action ; but the blood sugar does not tend to rise again, showing that the recovery process after insulin is dependent on the liver (cf. p. 423).

2. Nitrogenous Metabolism.—(*a*) *Urea.*—Estimations of urea concentrations in blood and urine have been carried out in hepatectomized dogs, which survived from 6 to 35 hours. (i) When urinary secretion is maintained, there is a steady decrease in the blood urea, *e.g.* to 6 mg. per 100 c.cm. ; the amount eliminated in the urine also shows a progressive and marked decrease. Practically all the urea excreted after hepatectomy can be accounted for by the decrease in the urea content of blood and tissues. (ii) If anuria follows the operation, the blood urea remains quite constant. (iii) If the kidneys are removed in a normal animal there is a rise in the blood urea ; if hepatectomy is now performed, the blood urea remains at the high level previously attained. These results prove conclusively that (in the dog) the *liver is the only site of urea formation*, and that urea once formed is not destroyed in the body.

(*b*) *Amino-acids and Ammonia.*—If amino-acids are injected intravenously into a normal animal, the level of amino-acid in the blood falls to normal in 2 hours ; 20 per cent. of the injected nitrogen is excreted in the urine as amino-acid, 25 per cent. as extra urea ; the rest is mainly diffused through blood and tissues as additional urea. If the procedure is repeated after hepatectomy, the blood amino-acid falls much more slowly, reaching normal after 6 hours. 33 per cent. is excreted in the urine as such, and the rest is found in the *muscles*, where the amino-acid concentration is much above the pre-injection level. Clearly injected *amino-acid is not destroyed* in the absence of the liver. There is no evidence that deamination (in the dog) can occur without the liver ; if the liver and kidneys are removed, there is but an inconsiderable increase in the ammonia content of the blood ; if the kidneys are intact, the ammonia excreted in the urine is above normal, but not to a great extent, and it is possible that this extra ammonia was manufactured in the kidney itself (p. 466) to maintain the blood reaction. Amino-acids cannot be converted into sugar after hepatectomy, for the injection of these acids does not counteract the hypoglycæmia.[1]

3. Bile Pigment Metabolism.—After total hepatectomy jaundice develops constantly in animals which survive longer than 6 hours. The plasma becomes yellow and the subcutaneous, pericardial, and mesenteric fat also become coloured. The blood gives a positive van den Bergh reaction for bilirubin (p. 202), first an indirect and then a biphasic reaction. The

[1] *Uric Acid.*—In most species of dog (cf. p. 440) uric acid is further broken down to allantoin ; it can be proved that this occurs in the liver. After hepatectomy, the blood uric acid rises from a trace to 2 or 3 mg. per 100 c.cm. ; if nephrectomy is carried out as well, the blood uric acid rises steadily to 7 or 9 mg. in 12 hours. If uric acid is injected into the hepatized animal it can almost all be accounted for by extra excretion by the kidney and by the raised concentrations in blood and tissues.

removal of the spleen and of all the abdominal viscera does not alter the rate of development of the jaundice. The injection of hæmoglobin increases the amount of pigment formed. These observations prove conclusively that bilirubin can be formed extra-abdominally (cf. p. 202). The sites of bilirubin formation can be studied by comparing the bilirubin content of the arterial and venous blood of the various organs; it thus shows that the tissues generally form no bilirubin. This process is limited to liver (negligible amounts), spleen (p. 201) and *bone marrow*, the last probably being the most important. If the gall-bladder is extirpated and the common bile duct tied, bilirubin accumulates rapidly in the blood (a definite rise is noted after *30 minutes*); after hepatectomy, the pigment accumulates just as rapidly, and if splenectomy is also performed the rate of manufacture of the pigment is not much modified either. The liver is thus mainly concerned with the *excretion* of bile-pigment; the elaboration of the pigment is chiefly carried out in the bone marrow, to a less extent in the spleen, and to a very slight extent in the liver (Kupffer cells).

There is no significant change in the blood *cholesterol* after hepatectomy.

4. Relation to Blood.—The liver appears to be the principal site of formation of *fibrinogen*. If the liver is injured (*e.g.* by the injection of small quantities of chloroform into the portal circulation) the blood fibrinogen is decreased and hæmorrhages tend to occur both externally and into the peritoneum; the clotting time is prolonged. As the liver recovers, the normal characters of the blood are restored. The liver manufactures red cells in the fœtus (p. 189), and may act in the adult as a storehouse of red corpuscles and of the material from which hæmoglobin is made (cf. p. 196).

5. Detoxicating Action (cf. p. 437).—The liver excretes certain poisons, *e.g.* heavy metals, dysentery toxin, ricin, into the bile. The conjugation of phenol with sulphate still takes place after hepatectomy; but the injection of phenol, benzoic acid, or phenoltetrachlorphthalein in amounts which normally produce little reaction may now prove fatal. The Kupffer cells of the liver are actively phagocytic and remove foreign particles from the blood stream.

Partial Extirpation of Liver.—In the dog, about 70 per cent. of the liver tissue may be removed without producing symptoms; the remaining tissue rapidly *proliferates*, so that the liver bulk is rapidly restored to its pre-operative level. To produce chronic hepatic insufficiency the following procedure is adopted: make an *Eck fistula* (p. 434)—the liver becomes reduced to half or less of its original size; within two months remove 60 per cent. of the liver. No regeneration now takes place, so that less than one-fifth of the original amount of liver tissue is left and very few of the cells which are present appear normal on histological examination. In spite of this, the animal maintains *fairly normal health*. These experiments illustrate the enormous physiological reserve in the liver, and how extensive disease of the liver must be before symptoms are noticed.

In these Eck fistula animals the chief abnormalities are as follows: (1) the blood sugar tends to be slightly below normal; (ii) after injection of insulin the recovery of the blood sugar is greatly delayed (p. 399 and p. 422); (iii) pancreatectomy produces only a *slight* hyperglycæmia, though the other symptoms of diabetes are present (p. 398 and p. 420); (iv) adrenaline produces a less marked rise in blood sugar (p. 129 and p. 398); (v) poisons are not well tolerated; (vi) nitrogenous metabolism and urea formation are normal.

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MOVEMENTS OF ALIMENTARY CANAL

Deglutition—Cardiac sphincter—Achalasia of cardia—Movements of stomach—Achalasia of pylorus—Vomiting—Small intestine—Ileo-cæcal sphincter—Large intestine—Defæcation—Hirschsprung's disease—Fæces—Constipation—Colic constipation—Dyschezia.

The movements of the alimentary canal in man are best studied by means of the X-rays after the ingestion of a meal which contains opaque barium salts.

Deglutition.—This is usually described in three stages—the first stage is voluntary, and the other two are reflex and involuntary.

1. After mastication, the food is rolled into a bolus and is moved to the back of the mouth by elevation of the front of the tongue. The mylohyoids contract, and the bolus is thrown back between the pillars of the fauces.

2. There are a number of sensitive spots on the posterior wall of the pharynx (supplied by the glosso-pharyngeal nerve) and accessory spots on the soft palate (ninth, and second division of fifth) and epiglottis (superior laryngeal). When these are mechanically stimulated, afferent impulses are set up, and reflexly through the medullary centres the following complex co-ordinated movement results: (i) The soft palate is elevated and the post-pharyngeal wall bulges forward to shut off the posterior nares. (ii) The posterior pillars of the fauces approximate to shut off the mouth cavity. (iii) The larynx is pulled up under cover of the root of the tongue, and the vocal cords are approximated. (iv) The epiglottis serves as a sloping ledge to guide the bolus past the laryngeal opening. (v) Respiration is inhibited. (vi) The superior constrictor muscles are relaxed to receive the bolus.

The swallowing reflex is temporarily abolished by anæsthetising the pharynx with cocaine; it is deranged by lesions of the medulla or of the ninth and tenth nerves. Food may then regurgitate into the nose or be aspirated into the larynx.

3. A peristaltic wave propels the food along the œsophagus. *True peristalsis* may be defined as a co-ordinated reflex in which a wave of contraction preceded by a wave of relaxation passes down a hollow viscus (Bayliss and Starling). The bolus thus finds that each successive part of the œsophagus first relaxes to receive it, and then contracts to drive it on.

The upper part of the œsophagus is striated, but the lower part is non-striated. Section of the vagus trunks produces complete paralysis of the

striated part of the œsophagus. Division of the plexus gulæ which lies on the surface of the œsophagus, prevents the peristaltic wave from being propagated beyond the site of section. If the œsophageal wall is divided but the superficial nerve plexus is left intact, the peristaltic wave can still pass normally over the œsophagus.

Reverse peristalsis may occur in the œsophagus, and is responsible in part for belching and acid regurgitation into the pharynx.

Cardiac Sphincter.—The last inch or more of the œsophagus, including the whole of the abdominal portion, is sphincteric in its action. The muscle coat is here thicker, and prominent longitudinal rugæ of the mucous membrane are visible. There is no great thickening of the circular fibres. When swallowing is not occurring the sphincter is in tone and the walls are tightly in apposition.

Within five or six seconds of swallowing the bolus, it reaches the lower end of the œsophagus, where its progress is momentarily arrested by the resistance of the closed sphincter. The sphincter then relaxes, but even now its lumen is considerably narrower than that of the rest of the œsophagus, and so food trickles slowly into the stomach. Relaxation of the cardia occurs with each œsophageal peristaltic wave.

When the whole of the meal has been eaten, the cardia remains shut to prevent the regurgitation of food, gastric juice, and gas, which would otherwise occur because of the positive intragastric pressure. According to Cannon, increased *acidity* of the gastric contents causes closure of the cardia ; the same effect is produced by a rise of intragastric pressure (Carlson).

If the intragastric pressure is excessively raised by rapid air swallowing (*aerophagy*) or by the evolution of CO_2 from ingested $NaHCO_3$, the resistance of the feeble cardiac sphincter may be overcome, and gas is expelled by the mouth.

Stimulation of the vagi causes tetanic contraction of the œsophagus. Section of the vagi in the neck results in temporary spasm of the cardia ; this is transient, however, and is soon replaced by marked relaxation of the sphincter. Strong stimulation of sensory nerves from the abdominal viscera reflexly (through the sympathetic nerves) produces spasm of the cardia.

Achalasia[1] **of the Cardia** (Cardiospasm).—This is a condition in which there is *failure of the co-ordinating mechanism* by means of which the cardiac sphincter is relaxed during swallowing. Food is consequently held up in the œsophagus, which becomes dilated. The muscle coat hypertrophies in an attempt to overcome the obstacle. When the contents of the œsophagus form a column eight inches high, the resistance of the cardia is overcome, and any excess food or drink above this height enters the stomach. The patient at first loses much weight, but finally reaches a state of equilibrium, as enough food enters the stomach to keep him alive on a low level of metabolism.

The cause of the condition is undetermined. It may be due to degeneration of the local nerves, or to impulses from some other part of the abdomen which reflexly prevent relaxation of the cardia. The condition may persist for many years if untreated ; it is often relieved by mechanical dilatation of the sphincter.

Morning sickness which occurs in alcoholic subjects is probably the bringing

[1] Achalasia=absence of relaxation.

up of mucus which has been secreted by the inflamed pharyngeal and œsophageal mucous membrane. This mucus *trickles* down during the night and, as it is not actually swallowed, relaxation of the cardia does not occur (Hurst).

Movements of the Stomach.—For purposes of description, the part of the stomach to the left of the incisura angularis is called the *cardiac* portion, and that to the right the *pyloric* part. The cardiac portion is divided into a part above the level of the cardiac orifice—the *fundus*, and a part below —the *body*. The pyloric part is divided into two parts—the pyloric antrum or vestibule, and the pyloric canal. Physiologically, the first part of the duodenum (duodenal *bulb* or cap) is associated with the pylorus. The pyloric canal is a channel, half an inch in length, which is normally closed by the tonic action of a well-developed *sphincter* muscle which surrounds it. Stimulation of the vagi produces variable effects on the stomach ; contraction is obtained if the initial tone is low, and relaxation if the initial tone is high, or mixed

Fig. 104.—Normal J-Stomach after Ingestion of 20 oz. of Barium. (Bennett, *Stomach and Upper Alimentary Canal.*)

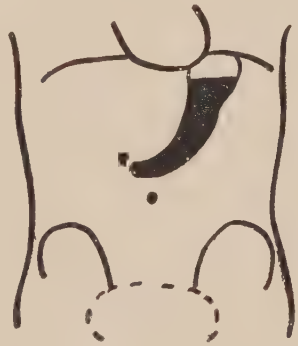

Fig. 105.—X-ray Appearance of "Cowhorn," or "Hypertonic" Stomach. (Bennett, *Stomach and Upper Alimentary Canal.*)

effects may be seen, *e.g.* contraction of one part of the stomach and relaxation of another.

The stomach displays postural activity or *tone*. When it is empty its walls are firmly in apposition. When food enters the stomach, the muscle fibres are elongated to enlarge the size of the cavity uniformly in order to accommodate the new contents, without much change of internal pressure (cf. p. 141). With an opaque meal of average composition, the stomach is J-shaped—the cardiac portion forms a vertical tube and the pyloric part forms a horizontal or slightly ascending segment which is turned to the right (Fig. 104). Sometimes the stomach is shaped like a "cowhorn"; the gastric axis is more oblique, and the pylorus is almost the lowest point on the lesser curvature (Fig. 105). Tonic activity of the stomach wall overcomes the influence of gravity, grips the contained food, and prevents the lower part of the stomach from sagging.

Peristaltic waves begin high up on the body of the stomach and follow

one another at intervals of about 20 seconds. They pass rapidly towards the pylorus, which, at this stage, is tonically contracted. After 3 to 12 minutes the sphincter relaxes so as to permit a small amount of chyme to escape. Contrary to what is usually claimed, the presence of acid in the stomach plays *no* part in opening the pyloric sphincter. In *achylia gastrica*, in which condition no free HCl is present in the stomach, the organ empties itself, as a rule, with excessive rapidity, and the pyloric sphincter tends to be patulous. It is stated that the presence of acid in the duodenum tends to close the sphincter. Thus too rapid evacuation of the gastric contents is prevented until the acid already discharged has been neutralized by the alkaline duodenal contents. This too, however, is disputed. In general it may be said that the pyloric sphincter behaves as would be expected from our knowledge of peristalsis—relaxation occurs as each wave of contraction involves the pyloric antrum. The "cardiac pouch"—*i.e.* the fundus and the upper part of the body of the stomach—is free from peristaltic waves and only exhibits tone. It presses the food slowly into the "pyloric mill," and so gradually diminishes in size. As pointed out previously (p. 386), when the stomach has emptied to a certain extent, the sphincter commences to relax also *between* peristaltic waves ; if the duodenal pressure then exceeds that in the stomach, or if anti-peristalsis occurs in the duodenum, *regurgitation* into the stomach may occur. When the stomach is empty, the pylorus may be relaxed for many minutes at a time, allowing free inflow of intestinal fluids (Bolton and Salmond).

After a fractional test meal the stomach is usually empty in about $2\frac{1}{2}$ hours. With the heavier and more solid barium meal, the stomach should be completely empty within 6 hours at the longest.

The *fasting* stomach exhibits rhythmic variations in tone, which increase and then diminish the pressure within the organ. These occur at the rate of three a minute. At intervals a series of powerful contractions occur which last about 30 seconds, and are associated with the appearance of the sensation of *hunger* (hunger pains) (Carlson). These changes were demonstrated by introducing into the stomach, *via* the œsophagus, a rubber balloon coated on the inside with barium paste. Both graphic and X-ray records of the stomach movements can thus be obtained.

The presence of an *ulcer* in the duodenum frequently upsets the normal pyloric mechanism and prevents the appropriate relaxation of the sphincter. As a rule the stomach in cases of duodenal ulcer is one that is naturally *overactive* and tends to empty itself rapidly. In the later stages of digestion, however, the gastric contents which are passed into the duodenum have reached a sufficiently high grade of acidity to irritate the ulcer and reflexly prevent relaxation of the pylorus.

Stimulation of any sensory visceral nerve increases the contraction of the pylorus and prevents its proper relaxation (Carlson). A *gastric ulcer* situated near the pylorus, disease of the *gall-bladder*, and chronic *appendicitis* may all act in the same way, and reflexly prevent pyloric relaxation and delay the emptying of the stomach.

Hypertrophic pyloric stenosis is a condition which occurs in young infants, usually boys, in whom for some unknown reason the pyloric sphincter is in a state of prolonged spasm. This overactivity leads to hypertrophy of the sphincter. Compensatory hypertrophy of the stomach wall develops in

order to overcome the obstacle. The passage of the peristaltic waves over the stomach may be visible through the abdominal wall.

Vomiting.—The phenomena of vomiting are as follows. Nausea is first experienced, the secretion of saliva is increased, and the breathing becomes deep, rapid, and irregular. *Retching* consists of simultaneous inco-ordinate spasmodic contraction of the respiratory muscles; the diaphragm, for example, descends when the expiratory muscles contract. The glottis closes and remains shut till the expulsion of the vomited material is effected. The pyloric part of the stomach contracts firmly, and at the same time the fundus relaxes so that the gastric contents are forced into the fundus; anti-peristalsis may occur sometimes in the stomach, but it is unimportant. The flaccid stomach is compressed by the raised intra-abdominal pressure which results from the simultaneous descent of the diaphragm and the contraction of the abdominal wall. The cardiac sphincter is inhibited and the gastric contents are therefore driven into the dilated œsophagus. Some of this material is at once expelled from the mouth; some is moved up and down the œsophagus. Towards the end of the act of vomiting, the diaphragm relaxes, *i.e.* ascends, and all the *expiratory* muscles and the abdominal wall contract. As the glottis is closed the pressure in the thorax now becomes *positive*. The œsophagus is thus compressed; it may also actively contract throughout its length or a wave of anti-peristalsis may pass over it, and its contents are thus emptied into the mouth. The posterior pillars of the fauces raise the palate and shut off the nasal cavity from the throat (Hatcher).

The complex series of movements which occur during vomiting are probably controlled by a group of nerve cells, in close relation to the vagal nucleus, called the *vomiting centre*. In the dog it is situated just in front of the calamus scriptorius. It is close to, but distinct from, the respiratory centre. If this centre is removed, the injection of apomorphine (which is a "central" emetic) no longer induces vomiting. Afferent impulses to produce vomiting may arise in the stomach and other parts of the gastro-intestinal tract, uterus, heart, and other organs. Certain drugs and poisons make the centre more sensitive, so that the normal impulses which reach it are sufficient to cause vomiting. In partial asphyxia and if the intracranial pressure is raised the vomiting centre is stimulated.

Small Intestine.—Two kinds of movements are carried out by the small intestine—*peristalsis* and *segmentation*.[1]

1. Peristalsis.—The first part of the duodenum (duodenal cap) retains the chyme sufficiently long for its neutralization to occur. The chyme is then conveyed by rapid peristaltic waves to the duodeno-jejunal junction, where a pause of a few seconds occurs; the occurrence of anti-peristalsis in the duodenum has already been referred to (pp. 385 and 404). The chyme is passed along the small intestine by a series of frequent and very rapid peristaltic waves which carry it on a few inches at a time. Each wave lasts about a second, and is followed by a quiescent period of a few seconds to a few minutes. An opaque meal cannot be followed through the coils of small intestine because it becomes too diluted by the fluid intestinal contents, but it is usually seen again when the ileo-cæcal sphincter is reached *three and a half* hours after the meal began to leave the stomach.

[1] If the abdomen of an animal is opened in a bath of warm saline, swaying or *pendulum* movements of the intestine can also be seen.

2. Segmentation.—A length of small intestine becomes divided by a series of constrictions into a number of small segments which are ballooned at the centre. Each segment is then divided in its middle (*i.e.* at the point of maximum distension), and the previous constrictions disappear. This occurs about six times a minute. Segmentation causes no forward movement of the intestinal contents; it helps to mix the chyme with the intestinal juices, and so aids digestion; it brings the chyme into intimate contact with the villi, and so aids absorption. It helps to squeeze blood and lymph out of the bowel, and so aids their return to the thorax.

The vagi end in Auerbach's plexus, which lies between the circular and longitudinal muscle coats. Stimulation of the vagi increases the tone of the intestine and renders the movements more active (after a preliminary but temporary inhibition). Stimulation of the sympathetic diminishes tone and arrests the peristaltic movements. After section of the vagi and destruction of the abdominal ganglia of the sympathetic, normal peristalsis may go on for months. Isolated strips of intestine suspended in a bath of warm oxygenated Ringer's solution will carry out rhythmic movements; according to Gunn, rhythmic contraction can still occur in such isolated strips after they have been deprived of their intrinsic nerve plexuses.

Normal *peristalsis* is probably due to a series of co-ordinated local nervous reflexes in response to the chemical and mechanical stimulation set up by the food. Axons from Auerbach's plexus reach the surface of the mucosa, and impulses can thus be transmitted down to the cells of the plexus and so to the muscle coats. Contraction occurs above the point stimulated and relaxation takes place below it.

Segmentation may be the response of smooth muscle to *distension*.

The intestinal movements may be influenced by the *ductless glands*—diarrhœa is a common symptom of exophthalmic goitre, and constipation of myxœdema.

Ileo-Cæcal Sphincter [Valvula coli].—This consists of the fusion of the circular and longitudinal fibres of the end of the ileum and of the adjoining cæcum; in addition, some independent specialized circular fibres are developed at the apex. Inspection in cases of cæcal fistula shows the sphincter as a smooth scarlet hemispherical papilla 1·8 cm. in diameter, which projects 1 cm. above the pink folded mucosa of the cæcum. The orifice is normally closed, and forms a dimple in the centre of the papilla. When a peristaltic wave passes over the terminal part of the ileum, the sphincter relaxes, about 1 drachm of fluid fæces mixed with a little gas escapes, and then the sphincter closes again.

In animals, section of the sympathetic causes permanent relaxation of the sphincter, and the contents of large and small intestine intermingle freely. Stimulation of the vagus is said to have no effect on the sphincter (Elliott).

In man, the main function of the sphincter is to prevent the contents of the ileum from passing too rapidly into the cæcum, as shown by the fact that an opaque meal may be present in the terminal ileum for about one hour before any appreciable quantity enters the cæcum. This delay permits of more complete digestion and absorption of the intestinal contents, so that the chyme which enters the cæcum contains scarcely any nutrient material.

As a rule peristaltic waves over the terminal ileum are infrequent, but when food enters the stomach a *gastro-ileal reflex* is set up, which produces active

peristalsis at the extreme end of the ileum, and chyme rapidly passes into the cæcum. In man, anti-peristalsis (*v. inf.*) in the ascending colon is feeble, and so there is little tendency for fæces to regurgitate into the ileum. The sphincter, however, is not capable of resisting considerable pressures. If a barium enema is administered at a pressure of 18 inches, or if powerful retrograde movements occur in the large bowel because of some mechanical obstruction, regurgitation into the ileum takes place.

Ileal Stasis.—Reflex achalasia of the sphincter may be set up by an inflamed appendix, and thus cause delayed emptying of the ileum.

Large Intestine.—As stated, the chyme reaches the terminal ileum 3½ hours after a meal, and is held up there for about 1 hour. The barium shadow can be first seen in the various parts of the large intestine the following number of hours after a meal: Cæcum, after 4½ hours; hepatic flexure, 6 hours; splenic flexure, 9 hours; descending colon, 11 hours; iliac colon, 12 hours; pelvic colon, 18 hours.

The cæcum and ascending colon are thought to play an almost entirely *passive* rôle, and fill solely as a result of the activity of the ileum, which occurs mainly during and immediately after meals. As a rule the contents of these parts of the large bowel appear immobile, but it is assumed that feeble peristaltic movements may occur. In animals a series of retrograde waves (*anti-peristalsis*) occur periodically which force the contents of the proximal colon towards the cæcum; such movements have occasionally been detected in man arising near the hepatic flexure, but they are both rare and feeble (Case).

Rhythmic variations of *tone* occur over all parts of the large intestine. They do not propel the contents onwards, but serve to mix them and aid absorption of water.

The colonic movements are more sluggish by night than by day.

Mass Peristalsis.—After each meal a *gastro-colic* reflex is set up. A brief, powerful peristalsis occurs in the colon, which constricts down, and its contents are driven vigorously onwards. By means of large forward movements of this type, the fæces reach the splenic flexure, then the descending colon, and finally the pelvic colon, where they accumulate. The fæces do not normally pass beyond the pelvi-rectal flexure—*i.e.* the point where the movable pelvic colon joins the fixed rectum at an acute angle. It is uncertain whether a definite sphincter exists here. Thickening of the circular muscle fibres is described (Symington), and narrowing of the lumen is present at this point in 80 per cent. of bodies. The normal rectum is quite empty, except immediately prior to defæcation.

About 350 grm. of fluid chyme passes through the ileo-cæcal sphincter daily (as observed in cases of cæcal fistula). The weight of the fæces is about 135 grm. on an average. Most of this absorption of water occurs in the cæcum and ascending colon, the contents of which are quite soft; little absorption occurs in the transverse colon, and none in the descending colon. The normal consistency of the fæces is due to further absorption which occurs in the pelvic colon.

Defæcation.—The gastro-colic reflex which occurs in the morning after breakfast, sets up in most normal people a wave of peristalsis over the distal part of the large intestine. The obstruction which is presented by the pelvi-rectal flexure is overcome, the sphincter presumably relaxes, and the fæces enter the rectum. A sense of fullness from distension of the colon is referred to

the front of the abdomen above the pubes. Distension of the rectum by the sudden entry of fæces gives rise, on the other hand, to a *perineal* sensation, and the desire to defæcate. If this desire is acceded to, a co-ordinated reflex results which empties not only the rectum, but every part of the bowel between the middle of the transverse colon and the anus.

The diaphragm descends, the glottis is closed, and the abdominal muscles contract. Waves of peristalsis pass over the distal part of the colon. The sphincter ani is relaxed and the fæces are evacuated through the narrow anal canal.

The sympathetic inhibits the whole of the large intestine and closes the sphincter ani. The parasympathetic innervation is less certain—the nervi erigentes probably supply the greater part of the colon with motor fibres, and relax the sphincter ani (p. 118).

Hirschsprung's Disease.—It is suggested that this condition is due to failure of relaxation (achalasia) of the pelvi-rectal or anal sphincters. The patients are children, usually boys, who from early childhood become progressively more constipated. The colon becomes enormously dilated and hypertrophied in an attempt to overcome the "functional" obstruction which is present. Defæcation may only occur at intervals of weeks or months.

The Fæces.—The fæces are not derived to any extent from the ingested food, but mainly from the secretions of the alimentary canal. They contain no soluble carbohydrate, peptone, or amino-acids. The fæces in starving animals do not differ in composition from those of normally fed animals, though they are diminished in amount. If vegetables and coarsely ground cereals are excluded from the diet, the fæces have a fairly constant composition, *i.e.* water, 65 per cent.; ash, 11 to 22 per cent.; ether-soluble substances, 12 to 18 per cent.; nitrogen, 5 to 9 per cent.

The *ash* consists mainly of calcium, phosphate, iron, and magnesia. The *ethereal* extract consists of fatty acids, a little lecithine, and a trace of neutral fat. Traces of cholalic acid and its decomposition product dyslysin, and coprosterol, which may be derived from cholesterol, are found. The material part of the fæces consists mainly of desquamated epithelial cells and numerous *bacteria*, most of which are dead.

Cellulose which is ingested passes out unchanged, and substances which are enclosed in a cellulose wall escape digestion and absorption. The increased bulk of this undigested residue stimulates intestinal peristalsis. The passage of the food through the bowel is therefore quickened, and the digestive ferments have insufficient time to exert their full action.

This is well illustrated by the following table (after Starling):

Diet.	Moist Fæces.	Dried Fæces.	Percentage of Ingested Food.	Nitrogen Lost.
Bread from fine flour .	132·7 grm.	24·8 grm.	4·0	2·1 grm.
Bread from coarse flour	252 ,,	40·8 ,,	6·6	3·2 ,,
Brown bread . .	317 ,,	76 ,,	12·0	3·8 ,,

It will be noticed that as the cellulose content of the food is increased, the bulk of the fæces is increased. They contain more water and solids; more of the ingested food is undigested and more nitrogen is lost to the body.

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CONSTIPATION

Constipation.—Hurst defines constipation as a condition in which none of the residue of a meal taken eight hours after defæcation is excreted within forty hours. Two main varieties are recognized:

1. Colic Constipation.—The passage of the fæces through some part of the colon is delayed, but the act of defæcation is normal. It may be caused by:

(*a*) *Deficient Motor Activity of the Colon.*—(i) The musculature may be congenitally thin; (ii) it is often atrophic in old people; (iii) in chlorosis and other anæmias the nutrition of the muscle may be disturbed; (iv) in febrile conditions the diet is bland, and provides little stimulus to the intestinal wall; there is also impaired secretion of the intestinal juices which form a very important constituent of the fæces.

(*b*) *Diminished Reflex Activity.*—(i) People who have no appetite take little food, and their gastro-ileal and gastro-colic reflexes are imperfectly aroused. Too little residue containing insufficient chemical and mechanical excitants of the colon is left in the bowel. (ii) The diet of civilized people contains too little cellulose; white bread is used and little green vegetables or fruit are eaten. (iii) Deficient excitability of the mucous membrane of the intestine results from inflammation (*e.g.* colitis), the long-continued irritation of purgatives, and the effect of astringents, especially the tannin of strong tea or black coffee.

(*c*) *Inhibition.*—(i) Stimulation of sensory nerves in animals produces reflex inhibition of the gastro-intestinal movements. Similarly, painful stimulation or injury of any part of the body, especially the abdominal and pelvic viscera, *e.g.* perforation of the stomach, biliary or renal colic, and torsion of the testis, inhibits intestinal movements. (ii) The sympathetic nerves may be directly stimulated, *e.g.* in acute pancreatitis, dissecting aneurysm of the aorta. (iii) Peritonitis directly paralyses the muscle wall of the intestine.

(*d*) *Uncontrolled and Irregular Action.*—*Spastic constipation* is a condition in which the colon distal to the hepatic flexure is contracted. The normal orderly propulsive movements of the bowel are absent, and are replaced by spasmodic contraction of some parts of the colon, while the others remain inactive. It may result from the action of lead, tobacco, and the presence of irritant material in the intestine. It is suggested that the intestinal crises of tabes are due to spasm; in this condition the colon may be felt as

a hard cord, and is so spastic that a barium meal cannot penetrate the contracted bowel.

(*e*) *Force* which is required to propel the fæces is excessive. (i) The lumen of the bowel may be narrowed by stricture, growth, diverticulitis, tubercle, etc.; (ii) the fæces may be dry and hard from insufficient drinking of fluid, excessive absorption of water by the large intestine ("greedy colon"), or loss through other channels, *e.g.* polyuria of diabetes, sweating in hot weather.

2. Dyschezia.—The fæces arrive normally at the pelvic colon, but their final evacuation is not adequately performed. If the call to defæcation is neglected, the rectal wall relaxes and the desire passes off. The rectum becomes in time excessively distended, the contractility of its walls is impaired, and evacuation becomes difficult even when a great effort is made. "*Fragmentary*" defæcation may take place—small amounts are passed, but much fæces is left behind in the rectum to continue distending it.

Causes.—i. Dyschezia is commonly due to laziness, ignorance, or fear of pain, *e.g.* because of inflamed piles. An unsuitable posture may be adopted during the act. When a proper position is employed, *i.e.* squatting with the thighs pressed on the abdomen, considerable compression of the intestinal contents occurs.

ii. The *defæcation reflex* may be feeble. In infants there may be congenital deficiency of sensibility in the rectum. The bowel may be anæsthetic as a result of organic nervous disease, *e.g.* tabes.

iii. Obstacles to defæcation may be present, *e.g.* hard and bulky fæces, spasm or achalasia of the sphincter ani (p. 408), fistula-in-ano, etc.

INTESTINAL OBSTRUCTION

High intestinal obstruction—Toxic proteose—Rôle of chlorides—Blood changes.

High Intestinal Obstruction.—If the small intestine is obstructed in its upper reaches, severe symptoms of intoxication set in and death results in a few days if the condition is not relieved. Recent experimental work has thrown much light on the condition.

A *proteose* has been isolated from the contents of the small intestine in cases of high intestinal obstruction which is absent from the normal bowel and which, if injected intravenously into normal animals, produces severe or fatal intoxication with marked prostration, repeated vomiting, and bloody diarrhœa. This proteose can withstand the action of the digestive ferments for over forty-eight hours, and, when given by the mouth, produces no symptoms whatever and is excreted unchanged in the fæces. This experiment proves that the intestinal mucosa is impervious to the proteose when it is ingested, and it is therefore suggested that the poison is formed *in the intestinal mucous membrane itself*. Some of the toxin passes into the blood and produces the symptoms of the disease, and some is excreted into the lumen of the bowel where it is quite inert (Whipple). It is suggested that the toxic proteose causes disintegration of tissue protein with the consequent liberation of nitrogenous bodies in greater amounts than the kidneys can deal with, for in cases of intestinal obstruction the blood urea and *non-protein*

nitrogen[1] are greatly increased in amount although the nitrogenous excretion in the urine is also increased.

Haden and Orr showed that, soon after obstruction of the duodenum or the upper ileum, there is a fall in the level of the *chloride* and a rise in the *bicarbonate* content of the plasma. The lowered chloride level is not due to vomiting, for it occurs even when no vomiting takes place. The chloride radicle is probably united with the toxic proteose to form a complex non-toxic body; the base which was previously united with the chloride (*e.g.* as NaCl) is liberated to combine with CO_2 to form bicarbonate, and an alkalæmia consequently develops (p. 226). It is suggested that if NaCl is given it neutralizes the primary toxic substance (*i.e.* the proteose) and thus prevents it exerting its baneful effects. Tissue breakdown therefore does not occur, and so the blood nitrogen is not raised.

$$\underset{\substack{\text{Toxic}\\\text{body}\\\text{(? proteose).}}}{X} + NaCl + H_2CO_3 \longrightarrow NaHCO_3 + \underset{\substack{\text{Non-toxic}\\\text{body.}}}{X.HCl}$$

(Haden and Orr.)

With the fall in the chloride of the plasma, the non-protein nitrogen begins to rise; but if NaCl is administered in adequate amounts as soon as the obstruction is produced it may prevent the development of the toxæmia and the blood nitrogen does not rise. Any symptoms that have already developed can be relieved by this treatment: thus one animal with complete obstruction was kept alive for twenty-eight days by this means. Water and glucose are of no avail, while bicarbonate makes the clinical condition worse by aggravating the alkalæmia and producing tetany. Obstruction of the intestine at the ileo-cæcal valve produces few symptoms.

If the terminal part of the ileum is anastomosed to the rectum and the intervening isolated portion of the colon is closed, no evidence of intoxication appears. The lower end of the closed colon is later found filled with a sausage-like mass having the appearance and consistency of normal fæces. No toxic proteose can be extracted from these fæces (Whipple). The toxic body thus appears to develop in the small intestine only. This explains why the symptoms in high intestinal obstruction are much more severe than in cases of obstruction of the large gut.

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INTESTINAL INTOXICATION

Intestinal intoxication—Putrefaction of Proteins—Products of bacterial action—Absorption of living bacteria—Mechanical and reflex results of constipation.

"Intestinal Intoxication."—It is still uncertain how many of the symptoms of constipation are produced. At present the most popular

[1] *i.e.* the nitrogen present in *all* the nitrogenous constituents of the plasma with the exception of the plasma proteins.

theory is that of intestinal auto-intoxication—*i.e.* that poisons are elaborated in the digestive tract as a result of constipation, and are absorbed through the mucous membrane and injure the individual. It has been demonstrated that poisonous bodies are formed in high intestinal obstruction, and it is known that the alimentary canal contains bacteria which under suitable conditions can produce disease. To prove the theory, however, it is necessary to show that a toxin is formed by bacterial or enzyme action in the digestive tract, in sufficient amounts to produce poisoning; that the toxin can be absorbed through the intestinal mucous membrane, that it is not further broken down to harmless bodies in the liver or elsewhere; and that repeated injection of the poison in small doses can produce symptoms resembling those supposedly resulting from constipation. It is merely necessary to define these criteria to show how far the theory of intestinal intoxication is from proof. Some of the possible causes of poisoning will be discussed.

1. There is no evidence that the constituents of the digestive secretions or the products of normal digestion produce poisonous effects; nor is there strong evidence, in spite of widely held views to the contrary, that a high protein diet is harmful. The Eskimos eat 8 lb. of meat or more daily in the seal-catching season, and are said to be a healthy race. It may be mentioned, too, that there is no experimental evidence that high protein diets cause damage to the kidney.

2. The products of fermentation of carbohydrates tend rather to cause diarrhœa in sensitive infants and children.

3. Putrefaction of Proteins.—i. As a result of putrefaction of protein, poisonous bodies—indol, skatol, and phenol—are formed. These are certainly absorbed to a slight extent and are excreted in the urine conjugated with sulphate. The fæces contain normally 60 mg. indol per 100 grm. of fresh material; as only 6 to 20 mg. indol are excreted in the urine in normal people (in the form of indican), it is evident that relatively little absorption occurs. Retention of fæces for days and weeks does not necessarily increase the urinary indican content. Large amounts of indican in the urine may occur in cases of renal insufficiency, liver disease, and in perfectly normal subjects. It seems, then, that the urinary indican is not a precise index of intestinal putrefaction. One gram indol, *i.e.* much more than is ever found in the bowel, has been given by the mouth to man without ill effect. Two grams, however, are said to produce fatigue, headache, and dizziness.

According to Benedict the blood phenol averages 5 mg. per cent. and is not definitely increased in any disease. The normal urinary phenol excretion is 0·2 to 0·4 grm. In the old days when carbolic sprays were employed during operations, much phenol was absorbed. Symptoms of fatigue and headache were only noted when 2 grm. phenol appeared in the urine.

ii. The low blood pressure which may accompany constipation has been attributed to *histamine* being formed in the bowel from histidine or some other precursor.

Histamine, however, can only be formed by a pure culture of certain bacteria; other organisms which are invariably present break it down as soon as it is formed (Mellanby). It cannot be absorbed except in minute traces from the intestine, and it is probably dealt with by the liver. If histamine were formed in any quantity, it would stimulate the bowel and

produce diarrhœa. In fact Abel regards histamine as an important physiological " tonic " to the bowel, stimulating the muscle coat, relaxing the local blood vessels, and increasing the secretion of the intestinal juices.

iii. It has been suggested that pressor bases, *e.g.* tyramine, isoamylamine, which have an adrenaline-like action, are formed in the bowel and produce a persistent hypertension. No definite results have been obtained from oral administration of these substances, though 200 mg. caused a slight rise of blood pressure after one hour. The liver rapidly detoxicates these bodies, and animals soon become quite resistant to them.

4. Products of Bacterial Action.—The fæcal bacteria are extremely numerous, forming 46 per cent. of the total nitrogen of the fæces.

They grow chiefly in the terminal ileum and in the ascending colon, where the fæces are liquid enough to form a suitable culture medium, but in the distal colon, owing to drying up of the fæces, most of the organisms die. The intestinal flora are fairly constant in make-up and are probably useful to the host in keeping out harmful bacteria which would otherwise gain a foothold. None of the organisms commonly found in the alimentary canal form any soluble toxins; few of them undergo dissolution to liberate endotoxins. Furthermore, toxic absorption can occur much more readily from fluid fæces than from dried hard material. It seems possible that excessive purgation, by keeping the fæces fluid, may be more harmful than the constipation for which it serves as treatment. There is more definite evidence that poisons can be absorbed in cases of *ileal* stasis. In a patient in whom one ureter was anastomosed to the small intestine, such severe symptoms developed from absorption of urine from the bowel that the kidney had to be removed.

5. Absorption of Living Bacteria.—Adami showed that the lymph nodes of the alimentary tract of healthy animals always yield cultures of intestinal bacteria, which are often found too in other organs. The organisms may pass by way of the lymphatics into the blood stream, but do not accumulate, as they are destroyed by the liver and spleen. It is conceivable that when stasis is present bacteria are absorbed from the fluid fæces in the cæcum and ascending colon in excessive numbers. They may collect together in various situations, where they are broken down and toxins are liberated which tend to damage the organ. Arthritis, fibrositis, rheumatism, etc., may thus result from what Adami calls " *subinfection*." Rosenow suggests that organisms of very low virulence may actually *grow* in the invaded sites (" latent infection ").

From this brief review it is clear that the evidence for intoxication from toxins or organisms absorbed from the intestine in cases of constipation is slight. It is possible, however, that infection may occur more readily when the intestinal mucosa is abnormal in some way. Starvation and purgation are said to facilitate the passage of bacteria through the mucous membrane. The administration of bile renders rabbits susceptible to invasion by typhoid bacilli given by the mouth.

Mechanical and Reflex Results of Constipation. — Donaldson experimented with healthy men who normally emptied their bowels once or twice daily. They ate an ordinary liberal diet and withheld from defæcation for ninety hours. Each subject developed the symptoms which are regarded as characteristic of " auto-intoxication," *i.e.* foul breath, furred tongue, impaired appetite, flatulence, nausea, loss of power of attention, depression,

restlessness, headache, insomnia, and irritability. A barium meal showed that the ileum was kept empty and that all the food remnants had accumulated in the colon. It is interesting to note that there was little increase in the urinary indican excretion. After an enema was administered and the bowel evacuated, the distress was promptly relieved, and in an hour or two the subjects felt quite normal again.

It is quite obvious that the symptoms complained of could not be due to toxic absorption, or else more time must have elapsed after evacuation of the bowel before the concentration of toxin in the body was sufficiently lowered. As Alvarez points out, " a drunken man is not immediately sobered when his whisky bottle is taken from him." The symptoms of constipation are largely due to the distension and mechanical irritation of the rectum (Alvarez). Masses of cotton wool or barium packed into the rectum produce identical effects.

It must be remembered that the rectum is very sensitive. A rise of internal pressure of 2 to 3 mm. Hg is perceptible, and a rise of 20 to 60 mm. Hg causes much distress. Sensory impulses from the bowel, it is well known, can easily influence the emotions and the mental processes—*e.g.* sleepiness after a meal, irritability and lack of concentration when hungry. A patient with a jejunal fistula always went to sleep if the intestine was made to contract actively by introducing a small balloon.

The feeling of " biliousness," the foul breath, and the coated tongue may be due to ripples of *anti-peristalsis* passing towards the proximal end of the gut. If the intestinal lumen is plugged, downward-moving peristalsis is slowed or stopped or even reversed. In this way gastric or intestinal contents may be deposited on the tongue (Alvarez).

The type of patient who is the subject of so-called " auto-intoxication " is usually keenly aware of what goes on in his body and responds strongly to visceral stimuli. Patients of a stolid type may go for weeks or months without passing a motion, and be able to eat well and do a good day's work. A case is recorded of a man who went from June 18, 1900, to June 21, 1901, without a motion. Towards the end of that time he belched a good deal and suffered from some pain. The abdomen was distended. He felt weak and lost some weight. After the colon was cleaned out he recovered rapidly.

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IX

METABOLISM

CARBOHYDRATE METABOLISM

Digestion—Absorption—Assimilation limits—Rôle of Liver—Glycosuria—Islets of Langerhans—Metabolism in diabetes—Diabetic coma—Insulin—Preparation—Action in normal subjects—Hypoglycæmia—Mode of action of insulin—Regulation of blood-sugar—Rôle of carbohydrate in diet.

Digestion.—1. *Ptyalin* of the saliva is a weak enzyme which only acts on starch after the cellulose envelope has burst, *e.g.* by cooking. It works in an alkaline or neutral medium, or, better still, if the reaction is feebly acid (pH6·5).[1] Ptyalin digestion thus continues in the stomach until it is arrested by the excessive acidity of the gastric contents. Its digestive action may thus be summarized :

Starch ⟶ erythro-dextrin ⟶ achroo-dextrin ⟶ maltose.
(Chiefly.) (To some extent.)

The HCl of the gastric juice hydrolyses cane sugar to some extent.

2. *Amylase* of the pancreatic juice rapidly converts all forms of starch completely into maltose. It acts in an alkaline medium, and is facilitated by the presence of the bile salts.

3. Succus entericus contains three ferments which act as follows :

Saccharose (Cane sugar.) —*Invertase.*→ Glucose + Lævulose.

Maltose —*Maltase.*→ 2 Glucose.

Lactose —*Lactase.*→ Glucose + Galactose.

The end products of carbohydrate digestion thus consist of *monosaccharides*, the most important of which by far is glucose.

[Intestinal bacteria may convert some glucose into methane and CO_2.]

Absorption.—The monosaccharides are absorbed into the portal vein and carried to the liver. Lævulose and galactose may there be converted into glucose ; as noted (p 397) this transformation cannot take place after hepatectomy. Most of the glucose is transformed into glycogen and stored in the liver as such. Some glucose passes through the liver into the systemic

[1] The reaction of saliva as secreted is faintly *acid* ; if the CO_2 in solution is allowed to escape by exposure to the air, the reaction becomes faintly alkaline (cf. Succus entericus, p. 426).

circulation. This can be well shown by means of a blood-sugar curve. 25 to 50 grm. glucose are ingested first thing in the morning before any food has been taken. Specimens of blood are withdrawn from a peripheral vein at intervals of half an hour, and their sugar content is estimated. The fasting blood-sugar level is 0·08 to 0·1 grm. per 100 c.cm. Half an hour after the glucose meal, it rises to about 0·14 or 0·16 per cent., owing to some of the absorbed sugar passing through the liver into the systemic circulation. During the next hour the blood sugar falls steadily to its original level as the tissues remove glucose for energy purposes, or for storage hin them as glycogen. The blood sugar may even fall *below* normal, owing perhaps to a compensatory secretion of insulin ; for if a second quantity of sugar is ingested the rise of blood sugar is not so great as previously.

Glucose is a *threshold* substance (p. 465) which is normally absorbed completely by the renal tubules from the glomerular filtrate. The renal threshold for glucose is 0·18 per cent., and if this level is exceeded in the plasma, a proportion of the blood sugar is allowed to escape in the urine in an attempt to lower the sugar of the blood to its proper concentration. If excess of a disaccharide, *e.g.* cane sugar, is ingested, some may be absorbed as such into the blood and be eliminated by the kidney.

After a large meal of starchy food, it is said that normal people may occasionally pass a trace of a reducing substance in the urine.

Assimilation Limits for Glucose.—(1) If 0·8 grm. glucose per kilogram body weight per hour is injected *intravenously* into animals, it can be utilized indefinitely and none appears in the urine. (2) If 0·9 to 2 grm. per kilogram are administered, some of the excess glucose is excreted in the urine. This fraction slowly increases to a maximum which, however, is only one-tenth of the glucose intake. It is interesting to note that the rate of absorption of sugar from the bowel never exceeds 1·8 grm. per kilogram per hour, so that little loss in the urine is to be expected following glucose ingestion in man (*v. inf.*). (3) If over 2 grm. per kilogram body weight are given, a large percentage of all the excess glucose over 2 grm. per kilogram appears in the urine.

When glucose is given by the mouth in *man*, the following results are obtained :

1. With 150 to 200 grm. glucose no trace of sugar is found in a twenty-four hour specimen of urine.

2. When 300 to 500 grm. are ingested, a proportion of subjects develop very *slight* glycosuria (*e.g.* 1 grm.). The blood sugar in these cases does not rise to the threshold value, but in spite of this a little sugar leaks out through the kidney.

When large quantities of sugar are taken, the stomach empties itself very slowly. Water is attracted into the stomach, and the glucose is held up there for some hours. It then passes slowly into the small intestine, and is absorbed gradually into the blood, so that the threshold level is not exceeded.

3. With amounts over 500 grm. the limits of *ingestion* are reached, as nausea and sickness develop. It may be noted that the B.P. glucose used clinically contains large amounts of dextrins and maltose. Pure glucose is very difficult to take, owing to its intense sweetness.

If after ingesting 100 grm. glucose, sugar is excreted in the urine in amounts sufficient to reduce copper solutions, it can be said that the subject

has *diminished sugar tolerance*. It is difficult to understand the meaning of the term *increased sugar tolerance*, which is so frequently used, for, as shown above, nausea develops before the limits of sugar utilization are reached.

Lævulose Tolerance.—According to Strauss, 90 per cent. of patients with disease of the liver pass lævulose in the urine after ingesting 100 grm. of this sugar. It is suggested that normally almost all the lævulose ingested is stored in the liver as glycogen.

Relation of Liver to Sugar Metabolism.—Glycogen is normally present in the liver of well-fed animals. After death it rapidly disappears, owing to the action of an enzyme which converts it into glucose. This reaction is a reversible one. The liver plays an important part in regulating the blood sugar level. (1) If much sugar is absorbed from the intestine, glycogen is deposited in the liver; it seems probable that the presence of insulin is necessary for this reaction. (2) If the systemic blood sugar tends to fall, liver glycogen is mobilized; this is due partly to impulses along the sympathetic nerves and partly to the secretion of adrenaline (p. 424). The liver glycogen is thus diminished by exercise, exposure to cold, starvation, injection of phloridzin (p. 418), and insulin hypoglycæmia in the intact animal. The injection of adrenaline, thyroxine, and pituitrin have the same effect. (3) The liver forms fresh sugar from protein—*i.e.* from the non-nitrogenous residues of many of the amino-acids (p. 420); this mechanism is chiefly responsible for the maintenance of the normal blood sugar in the starving person, and for the high blood sugar in the diabetic. Sugar formation from protein is checked by insulin (see also Extirpation of Liver, p. 397).

Sources of Liver Glycogen.—These are determined by administering various foodstuffs after emptying the liver of its glycogen by starvation combined with vigorous activity in a cold damp room, repeated cold baths, and injections of phloridzin eight-hourly. The following results are obtained:

(i) The ordinary carbohydrates of the food increase the liver glycogen.

(ii) Pentoses, cellulose, inulin and fat give negative results.

(iii) Conflicting results have been obtained with protein; as protein can give rise to sugar in the body there is no reason to doubt that this sugar may also be stored as glycogen. Usually, however, it appears that the ingested protein is converted into sugar only as rapidly as the body needs it.

After strychnine convulsions in a fasting animal, the liver is glycogen free. If the animal is allowed to sleep, fresh glycogen is formed, probably from tissue protein, as carbohydrate is not available.

Glycosuria.—This term refers to the presence of sugar in the urine in sufficient amounts to reduce copper solutions. The following causes must be discussed:

1. *Alimentary, i.e.* after the ingestion of carbohydrate. As seen above, this does not occur in normal subjects when polysaccharide is ingested and only to a trivial extent after the consumption of large quantities of glucose.

2. From *rapid mobilization of liver glycogen* with resultant hyperglycæmia. This follows injection of *adrenaline, pituitrin, thyroxine*, in *asphyxia* and during *anæsthesia*. Glycosuria may thus occur in conditions of emotional stress (p. 132), in exophthalmic goitre (p. 156), and in one stage of acromegaly (p. 150). Adrenaline may raise the blood sugar after exhaustion of the liver glycogen—so possibly it stimulates glucose formation from protein; but it does not act after hepatectomy (p. 398).

Puncture of the floor of the fourth ventricle (Claude Bernard) causes glycosuria, which appears to be due to impulses passing down the splanchnic nerves, partly to the adrenal medulla liberating adrenaline, and partly directly to the liver. It is prevented by section of the splanchnic nerves.

3. Extirpation or disease of the *pancreas* (*v. inf.*).

4. *Phloridzin* is a glucoside which is extracted from the cortex of the root of the apple tree. If it, or its derivative *phloretin*, is injected, glycosuria results, although the blood sugar is *below* normal. It has a specific effect on the renal epithelium. If cannulæ are inserted into both ureters and phloridzin is injected into one renal artery, sugar appears in the urine on that side within two minutes, but not till after ten minutes on the other side. It is suggested that phloridzin paralyses the power of the tubules to absorb sugar, which consequently escapes in the urine.

5. *Renal* glycosuria is a harmless condition in which the renal threshold is lowered. Small amounts of glucose are excreted, although the blood sugar does not reach 0·1 per cent.

Islets of Langerhans. — Scattered between the ordinary alveoli of the pancreas are small clumps of epithelial cells which are free from ducts, and are supplied by large convoluted capillary vessels. These *islets of Langerhans* contain two kinds of cells distinguishable by the character of their granules, which can be demonstrated by intra-vitam staining with neutral red : α granules are fixed in alcoholic solution, while the β granules are fixed in watery solutions. The latter granules are said to be altered in disease.

The islets are believed to elaborate an internal secretion, *insulin*, which enables the tissues to *burn* sugar and *store* it as glycogen ; insulin also *inhibits sugar formation from protein in the liver*.

Evidence for Secretory Nature of Islets. — 1. Minkowski and Mehring showed that excision of the pancreas causes severe and rapidly fatal diabetes. The operation is carried out in two stages : (i) the greater part of the gland is removed and a part of the tail is transplanted under the skin. No glycosuria develops, and the abdominal wound rapidly heals. (ii) The transplant is removed later by a simple skin incision. In a few hours the urine contains 5 to 10 per cent. sugar, and the animal usually dies of coma within three weeks.

2. The pancreatic ducts are ligated or blocked. The externally secreting tissue disappears, and the pancreas is converted into a thin strip of connective tissue which still contains the islets. Removal of this strip results in intense diabetes.

3. In diabetes mellitus in man gross macroscopic changes in the pancreas are not commonly found, but if the pancreas is examined histologically within a few hours of death, it is said that œdematous changes are found in the β cells of the islets (Allen).

4. The active principle *insulin* can be extracted from the pancreas under suitable conditions and also from pure islet tissue.[1]

Metabolism in Diabetes. -Diabetes mellitus is a disease in which profound disturbances of metabolism occur owing, presumably, to insufficient secretion of insulin by the islets of Langerhans.

1. Carbohydrates.—As stated, insulin is necessary for the utilization

[1] Cf., however, p. 422.

of sugar as a source of energy and for its conversion into glycogen. In diabetes—

i. The resting blood sugar is higher than normal.

ii. After a carbohydrate meal it rises above 0·18 per cent. and sugar appears in the urine. The blood sugar may reach 0·3 to 0·5 per cent. in a severe case, because the liver does not store the normal proportion of the absorbed sugar as glycogen, but allows it to pass through in excessive amounts into the systemic circulation.

iii. As the tissues do not remove sugar from the blood, the blood sugar falls very gradually, as the sugar is eliminated in the urine.

iv. As sugar is present in excess in the blood, it is not completely reabsorbed by the tubules in the normal manner. As the tubules still absorb water, the percentage of sugar in the urine may rise to 5 per cent. or higher. The osmotic pressure exerted by this high concentration of sugar hinders the absorption of the usual quantities of water, and so *polyuria* results (p. 471). Owing to the excessive loss of water from the body, great *thirst* is experienced.

v. Glycogen disappears from the liver and to a lesser extent from the muscles. It is said, however, that the glycogen stores in the heart are actually increased.

vi. As sugar is not utilized, the respiratory quotient falls from the normal 0·8 or 0·85 down to 0·7, *i.e.* that associated with the combustion of fat only.

2. Fats.—i. For the complete oxidation of fat, sugar must be available in a utilizable form. Consequently, in diabetes the fats are only broken down to the four carbon stage, *i.e.* β oxy-butyric and aceto-acetic acids. These substances pass into the blood causing a *ketosis* (p. 219), and are buffered by the $NaHCO_3$ of the plasma. The tendency to acidæmia is dealt with in the usual ways:

(*a*) Compensatory hyperpnœa, with resulting fall of the alveolar and therefore of the arterial CO_2.

(*b*) Excretion of highly acid urine.

(*c*) Increased NH_4 excretion: more of the NH_3 formed in the liver from amino-acids is used to neutralize the abnormal acids and less is converted into urea or more NH_3 is made by the renal cells. Direct measurement of the H ion concentration of the blood in most cases of diabetes reveals little change, proving how completely compensation is effected.

ii. β oxy-butyric acid is a relatively harmless substance. Aceto-acetic acid in virtue of its *enolic* form $CH_3COH{=}CH.\ COOH$, is highly poisonous. When present in large amounts it stimulates the respiratory centre,[1] causing very deep breathing ("air-hunger"), and depresses the higher centres, causing loss of consciousness (coma).

iii. Aceto-acetic acid is disintegrated in the bladder and in the lungs, giving off CO_2; acetone is left which is eliminated in the expired air and excreted in the urine.

iv. Owing to tissue starvation, the fat of the depots is called upon. It is transported to the liver to be desaturated and to be converted into lecithine-like bodies which the tissues can use. There is excess of fat in the blood (up to 12 or even 24 per cent.); the blood cholesterol also rises (to 1·5 or even

[1] Any compound, whatever its reaction, which contains the enol group, $COH{=}CH$, stimulates the respiratory centre.

3·5 per cent.) (*lipæmia*). If the lipæmia is attributed solely to the demands of the cells for a source of energy, it is somewhat strange to find that the hungry cells do not remove the fat from the blood as rapidly as it is offered. The liver is depleted of its glycogen, but is loaded with fat.

v. The *glycerol* ($CH_2OH—CHOH—CH_2OH$) of fat is excreted quantitatively as glucose.

3. Protein.—Protein metabolism is very seriously disordered.

i. In a starving diabetic, the blood sugar remains high, and sugar is still excreted in the urine. This sugar is probably not formed from fat. The conversion of fat into glucose requires large amounts of oxygen, and results in a low respiratory quotient, *e.g.* 0·4 (see p. 430). In the diabetic the R.Q. does not usually fall below 0·7, thus excluding this hypothesis. Some workers have obtained low readings for the R.Q., and so the formation of glucose from fat cannot be wholly negatived. In the main, the blood sugar of the starving diabetic is derived from tissue protein.

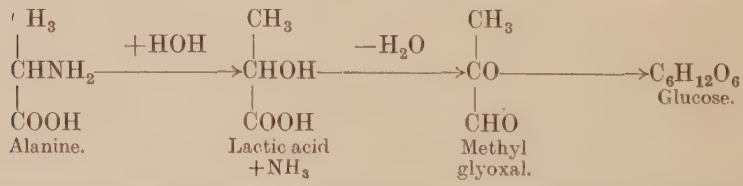
ii. In the starving diabetic, once the carbohydrate stores are exhausted, a constant ratio is attained in the urine between the sugar (D) and the nitrogen (N) excreted. The D : N ratio is about 3·6. The fact that there is a *constant* ratio suggests that the sugar and nitrogen are coming from a common source, which can only be tissue protein. If a protein meal is administered, both the N and the D excretion are increased, but the D : N ratio still remains the same, confirming the suggestion just made. It is found that *60 per cent.* of the carbon of the ingested protein is converted into, and eliminated as, sugar.

iii. Certain amino-acids, *e.g.* glycine, alanine, cystine, aspartic and glutamic acid, are excreted quantitatively by the diabetic as glucose. If leucine, tyrosine, or phenyl-alanine are administered, they do not affect the sugar excretion but increase the amount of *ketone* bodies formed. It appears that after the NH_3 has been removed from the amino-acids, the acids left follow one of two paths :

(*a*) Most of the amino-acids are converted into and excreted as glucose.

(*b*) Some of the aromatic acids give rise to ketone bodies (cf. p. 435).

It is found that both lactic acid and methyl glyoxal are excreted as sugar.

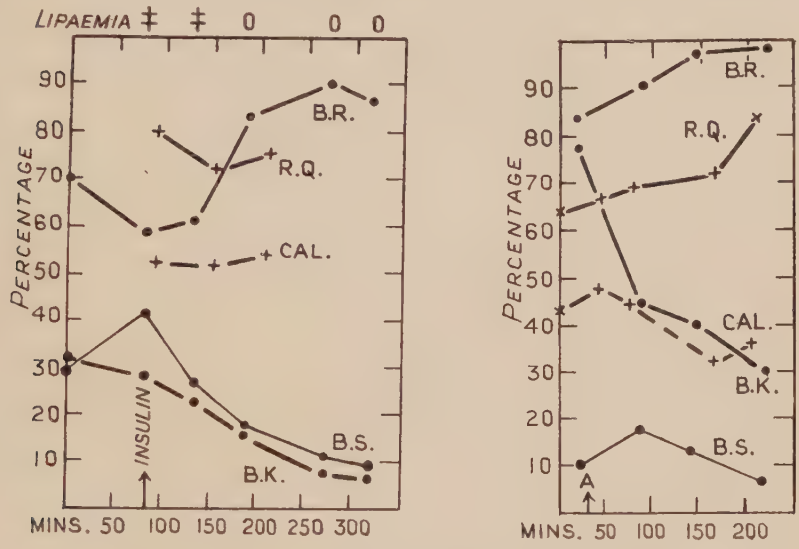


This gives us a clue as to how alanine is converted into glucose. It is first deaminized to form lactic acid ; then loses one molecule of water to form methyl glyoxal. Two molecules of the latter are condensed together with two molecules of water to form glucose. If hepatectomy is performed in the diabetic animal *hypo*-glycæmia develops, proving that the liver is the site of sugar formation from protein in the diabetic as in the normal animal (p. 398).

In considering the diet of a diabetic, *all* the carbohydrate, *60 per cent.* of the protein, and *10 per cent.* of the fat (glycerol) ingested must be regarded as equivalent to sugar.

The R.Q. in a severe case of diabetes is 0·7, because the only substances which are burnt are fat and the moiety of the protein molecule which goes the way of fat metabolism. Great bodily wasting occurs. The voracious *appetite* is due to the intensity of the hunger contractions of the stomach and not to the under-nutrition. Considerable *asthenia* is present.

Diabetic Coma.—The onset of coma is foreshadowed by certain clinical manifestations, *e.g.* headache, nausea, vomiting, obstinate constipation, and abdominal pain. The breathing becomes deep and sighing ("air



FIGS. 106 and 107.—Action of Insulin in Diabetic Patients.

B.R.=Bicarbonate content of plasma (100 on ordinate=normal, *i.e.* about 52 vols. per cent.). R.Q.=Respiratory quotient. Cal.=Calories per hour, calculated from respiratory exchanges. B.S.=Blood sugar percentage. B.K.=Blood ketone bodies in mgrms. per cent. R.Q. and B.S. have been multiplied by 100 in order to show them by means of the same scale of ordinates. Abscissæ=Time in minutes from commencement of observation. Degree of lipæmia is indicated by the signs ‡ or 0 at top of chart.

FIG. 106.—Case of Severe Diabetes with carbohydrate tolerance of 10 grms. daily. Insulin, 30 units at point shown (patient fasting). Note marked rise of B.R. from 59 to 91 per cent. of normal in 3 hours, and fall of B.S. and B.K.

FIG. 107.—Fasting Diabetic. Insulin 10 units and glucose 20 grms. at A. There was no lipæmia in this case. The B.S. rose because of ingested glucose and then fell; note rapid diminution of B.K. and rise of R.Q. in this case. (Davies, Lambie, Lyon, Meakins, and Robson, *Brit. Med. Journ.*, 1923.)

hunger"), and consciousness is gradually lost. If the alveolar CO_2 falls below 2 per cent., coma may supervene within twenty-four hours. The factors producing the coma are:

1. Accumulation of the poisonous aceto-acetic acid.
2. Possibly the slight acidæmia which may be present (Cullen).
3. Failure of the kidneys—albuminuria, casts, diminished excretion of urine, and high blood urea may be present.

The administration of insulin to a diabetic provides the factor that was lacking, breaks the vicious circle, and restores the normal state of affairs. The action of insulin in the diabetic is well illustrated in Fig. 106. The

blood sugar is lowered rapidly, the ketone bodies are greatly diminished, the lipæmia disappears, and the bicarbonate content rises to about normal. The increased combustion of glucose tends to raise the respiratory quotient; but some of the CO_2 formed in the tissues is *retained in the blood* to unite with the base freed consequent on the removal of the ketone bodies. In this way the rise in R.Q. may be masked or converted into a fall. If insulin is given *together with glucose* the ketosis is disposed of more rapidly, for it is believed that combustion of adequate amounts of glucose must occur for fat metabolism to proceed to completion; this is seen in Fig. 107 in which a definite rise of R.Q. was produced by insulin.

Insulin.—Insulin was discovered by Banting and Best in 1922.

1. PREPARATION.—It is essential that the pancreatic trypsin be first destroyed, for otherwise it would break up insulin.

i. *Alcohol Method.*—Fresh or frozen pancreas is mixed with an equal amount of 95 per cent. alcohol, making an alcohol concentration of about 50 per cent. which destroys trypsin. The filtrate is removed, concentrated, and alcohol added to increase its strength to 80 per cent., at which point the inactive proteins are precipitated. More alcohol is added, and at 95 per cent. alcohol, *insulin* is precipitated.

ii. *Acetone Picrate Method.*—Picric acid precipitates all the proteins of the pancreas and insulin as picrates. The insulin picrate is alone soluble in acetone, and can be separated in that way. It may then be converted into the insulin hydrochloride, in which form it is usually employed clinically.

Insulin can be extracted from the blood and from all the tissues of man. It is remarkable that insulin can be obtained from all the tissues—including the *pancreas*—of patients dead of diabetes and from the tissues of depancreatized animals.

2. PROPERTIES.—Pure insulin has probably not yet been isolated, as it is always adsorbed to protein. It is a white powder, soluble in water, and stable in acid solutions to mild oxidizing and reducing agents. It is rapidly destroyed by pepsin and trypsin. It contains no phosphorus, but a good deal of sulphur. It is not an albumose, and some specimens have been prepared which do not give the biuret reaction. Abel has recently obtained a crystalline preparation of insulin, and finds that it is related chemically to the amino-acid cystine.

Action in Normal Subjects.—Subcutaneous injection of insulin results in a fall in the level of the blood sugar. This effect comes on within a few minutes, and reaches its maximum after one-half to several hours according to the dose employed.

Hypoglycæmic Symptoms.—When the blood sugar content is very low, certain striking symptoms become manifest which vary in different species.

i. In *rabbits* at a blood-sugar level of 0·045 per cent. there is loss of muscle tone, violent convulsions at intervals, rapid shallow breathing, and subnormal temperature. Later, death results in coma from respiratory failure. The convulsions are due to the fall of blood sugar stimulating centres in the *pons* and *medulla*; convulsions can still occur in the decerebrate animal, but not after the medulla has been destroyed. (Cf. Hypoglycæmic symptoms in dogs following extirpation of liver, p. 397.) If the dose of insulin is not too

large the blood sugar returns to normal owing to mobilization of the liver glycogen. Hypoglycæmia is therefore most pronounced and prolonged if the liver glycogen stores are low; recovery of the blood sugar does not occur after hepatectomy (p. 399). The liver is stimulated *via* the sympathetic nerves and by the liberation of adrenaline (p. 424).

ii. In *man* the sequence of events is as follows:

α. Feeling of extreme hunger; a great sense of fatigue, so that walking becomes difficult. The patient may become anxious, worried, or excitable. It is very important to note that some patients during a hypoglycæmic attack behave as if they were intoxicated with alcohol or demented.

β. Tremulousness develops, and fine movements cannot be carried out, *e.g.* knitting becomes impossible.

γ. Vasomotor disturbances—flushing and profuse perspiration which soaks the bedclothes, or pallor and a sense of chilliness.[1]

δ. Finally, mental disturbances, delirium, and coma, with loss of the deep reflexes. Symptoms may set in at a blood sugar level of 0·075 per cent., or not till a much lower level, *e.g.* 0·032 per cent., is reached. In chronic diabetics with high blood sugar, symptoms may occur when the hyperglycæmia is suddenly lowered, *e.g.* to 0·15 per cent. (cf. p. 398).

The symptoms of hypoglycæmia may be relieved by the following methods, all of which act by raising the blood-sugar level:

i. Administration of *glucose*. The other hexose monosaccharides, *e.g.* mannose or lævulose, are relatively ineffective. In animals 2 grm. glucose per kilogram of body weight given subcutaneously or intravenously results in dramatic recovery in a few minutes (cf. p. 397). Clinically, in a conscious subject, an orange may be eaten and is usually effective; in an unconscious patient, glucose is given per rectum or intravenously.

ii. *Adrenaline* acts by mobilizing the liver glycogen. It is more effective in a well-fed animal than in a starved or diabetic subject, in whom the glycogen stores of the liver are low.

iii. *Pituitrin* injected together with insulin prevents the latter from acting; it abolishes insulin convulsions and raises the blood sugar (p. 148).

Other Inter-Relations.—(i) After removal of the thyroid the animal is more sensitive in its reaction to insulin. (ii) Animals in œstrus and women during menstruation are more resistant to insulin (p. 171). (iii) There is no difference between the adrenalectomized and normal animal in its response to insulin. This indicates that the adrenals are not linked up with the pancreas in the control of sugar metabolism.

Ether-hyperglycæmia is prevented by insulin, which should be administered before any surgical procedure is employed in a diabetic subject.

Mode of Action of Insulin.—(i) The problem can first be studied on a simplified preparation the *decapitated and eviscerated animal* (in which the intestines are removed and the liver blood vessels ligatured). The preparation thus consists essentially of heart, lungs, and muscles; hypoglycæmic convulsions cannot occur[2] and the results are not complicated by absorption of sugar from the intestines, excretion by the kidneys, or compensatory reac-

[1] Some of these symptoms may be due to the secretion of adrenaline which occurs (p. 424).

[2] Because the brain stem has been destroyed.

tions by the liver. Glucose is administered intravenously at a constant rate so as to maintain a *high* level of blood sugar, and insulin is then injected. It is found that as a result sugar disappears at an increased rate from the blood. There is a rise in the O_2 consumption and the CO_2 output, and the R.Q. of this *excess* metabolism over the resting values is 1 (cf. p. 359). The excess respiratory exchanges, however, may only account for about 25 per cent. of the glucose which disappears from the blood stream ; probably all the rest of the sugar which had not been accounted for is deposited in the muscles as *glycogen*. Insulin thus creates a craving in the tissue cells for sugar, which is used in preference to other foodstuffs, and is also deposited as glycogen (Dale). These effects of insulin are probably due to a direct action on the muscles. Insulin also accelerates sugar utilization in the perfused limb, and increases deposition of glycogen in the isolated perfused heart.

(ii) When insulin is given to *intact* animals the results are more complicated.

(*a*) There is first increased utilization of sugar by the tissues and increased storage of glycogen by the muscles and probably also by the liver ; the metabolism is increased and the R.Q. rises. This more rapid removal of sugar from the blood is not, however, a complete explanation of the hypoglycæmia in the intact animal, as will appear from the following considerations. If a starved animal, with exhausted liver glycogen, is made to carry out severe exercise, sugar is presumably removed from the blood in large amounts, but in spite of this there is no fall of blood sugar ; clearly the blood sugar level is being maintained from some other source, and from all the evidence it is clear that sugar is being made from protein in the liver (p. 398). If this function of the liver were unaffected by insulin the sugar formed there would prevent the hypoglycæmia. It is suggested, therefore, that insulin *paralyses sugar formation from protein* ; by causing the tissues to remove the sugar from the blood and preventing the liver forming fresh sugar a marked fall of blood sugar is produced by insulin. One can picture, therefore, that the hyperglycæmia of the diabetic is partly due to the excessive, wasteful, and unchecked manufacture of sugar from protein in the liver.

(*b*) The onset of hypoglycæmia affects the central nervous system and impulses pass out along the sympathetic nerves to the liver and to the adrenal medulla to *mobilize liver glycogen* and retard the fall in the blood sugar. Cannon (using the denervated heart preparation, p. 131) found that at a certain critical level of blood sugar adrenaline is secreted to reinforce the nervous messages which pass directly to the liver. If the nerves to the adrenal are severed, the hypoglycæmia produced by insulin is more profound and more slowly recovered from. If the sympathetic nerves to the liver and adrenals are paralysed by ergotoxin, no mobilization of liver glycogen occurs ; one then finds increased amounts of glycogen in the liver (due to the direct action of insulin), and a very slow recovery of the blood sugar, because the compensatory mechanism does not come into action. If the liver is extirpated (p. 399), there is no recovery of the blood sugar after an injection of insulin. In an intact animal killed with insulin, the liver glycogen is usually much *lower* than normal (*e.g.* 1·8 per cent. instead of 5·5 per cent. in one experiment) as both the glycogen originally present and that stored under the influence of insulin is mobilized by the nervous system and adrenaline.

(*c*) The glycogen stored in the muscles is used up to a large extent if

convulsions take place; if the motor nerves to the muscles are severed, increased glycogen storage under insulin can be demonstrated in the intact animal.

(*d*) If a large dose of insulin is administered when the carbohydrate reserves are low death may result. In the terminal stages the metabolism is depressed and the temperature may be subnormal because of the inadequate supplies of sugar to the tissues.

(*e*) A rapid fall of the inorganic phosphorus of the blood accompanies the fall of blood sugar. It has been suggested that some of the glucose combines with phosphate to form a *hexose diphosphate* which is deposited in the tissues. Little, if any, increase of this compound in the muscles can, however, be demonstrated. The phosphorus excretion in the urine is diminished.

(*f*) Animals dying in hypoglycæmia pass very rapidly into rigor mortis. The reaction of the muscles is *alkaline* and the lactic acid content is very low. The cause of the rigor is unknown, but it is associated with the low muscle glycogen.

Regulation of Blood Sugar.—As there are only 5 grm. of sugar in the whole blood stream, the controlling mechanism must be very perfect to succeed in preventing all but minor fluctuations in the level of the blood sugar under almost all conditions, particularly when one remembers what large quantities of carbohydrate may be ingested or removed from the blood by active tissues. The principal factors concerned are: (i) *Alimentary canal*: ingested polysaccharides are slowly broken down into glucose, so that absorption is never very rapid (p. 415). If glucose is ingested in large amounts it is held up for a considerable time in the stomach, and if taken in still greater quantities it is rejected by vomiting (p. 416). (ii) The *liver* can store about 150 grm. of sugar as glycogen; it mobilizes sugar when needed and forms sugar from protein (p. 417). (iii) *Insulin* regulates liver activity and controls the utilization and storage of sugar by the tissues. If any considerable change in the blood sugar occurs, symptoms are produced: those of hypoglycæmia have been described above (pp. 397, 422); those of hyperglycæmia are not so definite, but it is generally believed that many of the clinical manifestations of diabetes—*e.g.* lowered resistance to infection, degenerative changes in the nervous system—are the result of the high level of blood sugar.

Rôle of Carbohydrate in the Diet.—1. It is a readily available source of energy. Each 1 grm. carbohydrate yields about 4·1 calories.

2. Its presence in a utilizable form is essential for the complete combustion of fat.

3. It is probable that the formation of lactic acid from glycogen is the essential step in the contraction of all forms of muscle—skeletal (p. 356), cardiac (p. 242), and smooth muscle.

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FAT METABOLISM

Digestion—Absorption—Blood-fat—Depot fat—Rôle of liver—Fat of tissues—Utilization of fat—Rôle of fat in the diet.

Digestion.—Stomach.—Some free fatty acid is present in the natural fats of the food, and the amount is increased by cooking and by the slight hydrolysis which occurs in the stomach. A fat-splitting enzyme—*lipase*—(identical in almost every respect with the lipase secreted by the pancreas) is present in the pure gastric juice from a Pavlov pouch. It is sensitive to free acid, and is destroyed by exposure to 0·02 per cent. HCl for fifteen minutes, so that its presence in the acid gastric juice can only be detected if the juice is neutralized while being collected, or if the acidity is lowered by the introduction of protein into the stomach. In addition, *pancreatic* lipase may regurgitate into the stomach from the duodenum. The activity of lipase in the stomach is obviously restricted : it may be of importance in cases of *achylia gastrica* and in young *suckling* animals which ingest large quantities of milk—the fat of the milk inhibits the secretion of gastric acid, it is present in an emulsified and therefore readily digested form, and the protein of the milk lowers the H ion concentration in the stomach.

Small Intestine. The main digestion of fat occurs in the small intestine, the active ferment being predominantly *pancreatic lipase* (which is assisted in many ways by the *bile*) ; the presence of fat in the bowel also calls forth a secretion of succus entericus which has a definite lipolytic action. The following properties of lipase are important : (i) it is rapidly destroyed *in vitro* by *trypsin* ; egg albumin has a protective action, however, and this may account for lipase acting in the presence of trypsin in the intestine ; (ii) it acts in neutral solutions the activity rapidly diminishes on the acid side of neutrality and increases up to a point on the *alkaline* side (and then falls off) ; (iii) *electrolytes* (NaCl, KCl, $CaCl_2$) increase its activity ; (iv) *bile salts* act on the enzyme itself, enhancing its digestive activity even up to fourteen fold. As neutral fat is insoluble in intestinal chyme, lipase operates at a great disadvantage at first, because it can only attack the surface of the oily mass. Each molecule of neutral fat is split into 1 molecule of glycerine and 3 molecules of fatty acid ; the fatty acid is then converted into *soap* by means of base which is obtained from the alkaline pancreatic and intestinal juices, and to a less extent from the bile.[1] In addition to providing base, the bile assists saponification (formation of soap) in a variety of ways. The *bile salts*, aided by *lecithine*, dissolve the fatty acids which are formed as a result of digestion, and the presence of bile accelerates the reaction between Na_2CO_3 and fatty acid. The soap forms a thin coating round the oily fat globules, prevents them running together, and thus converts the fat into an *emulsion* with numerous surfaces which can be readily attacked by lipase ; hydrolysis can then proceed very rapidly. The final products of intestinal digestion are glycerine, soaps, and fatty acids dissolved in bile : normally the hydrolysis

[1] The reaction of the intestinal contents determined with the hydrogen electrode and with precautions *to prevent loss of* CO_2 is definitely acid (pH 5·6–6·6 in ileum of dogs) in animals and man (M'Clendon). This does not, however, preclude the formation of soaps, for regions of alkalinity are probably present close to the villi where absorption takes place.

is very complete. The substances mentioned are then taken up by the lining epithelium of the small intestine. Bile plays an important part in absorption, partly because of its solvent action, and perhaps by altering the permeability of the epithelium of the villi ; it is interesting to note that bile increases the diffusibility of fatty acids (and of neutral fat) through collodion membranes. Exclusion of the bile results in a greater loss of fat from the bowel than exclusion of the pancreatic juice ; the fat is extensively hydrolysed but imperfectly absorbed, and so appears in the fæces as fatty acids and soaps (cf. p. 392).

Absorption.—*Resynthesis of neutral fat* then takes place in the epithelium of the villi : (i) at the height of fat absorption there is an increased amount of fatty acid and of neutral fat in the mucous membrane of the intestine, the latter predominating ; (ii) if free fatty acids are administered (emulsified with a little soap and protein) they can be recovered as neutral fat in the chyle. It is possible that during the process of resynthesis some *modification* of the fat takes place : if saturated fats are taken, a fat of higher iodine value (*i.e.* more unsaturated) is found in the chyle, and with unsaturated fats, a fat of lower iodine value (*i.e.* more saturated) is obtained. How this process occurs is obscure, but it may be due to differences in the degree of absorption of different fatty acids : thus, if free fatty acids are fed in a palatable form the degrees of absorption are stearic acid, $C_{18}H_{36}O_2$—35 per cent. ; palmitic acid, $C_{16}H_{32}O_2$—78 per cent. ; oleic acid, $C_{18}H_{34}O_2$ (one unsaturated linkage) —98 per cent. Insoluble substances—*e.g.* finely emulsified *paraffin*—are not absorbed.

The process of absorption may be studied *histologically* by staining sections of intestine with osmic acid after a large fat meal. No stainable fat can be demonstrated in the free striated border of the epithelial cells lining the villi. In the deeper parts of the cells, fat globules appear which rapidly enlarge till they occupy the greater part of the cell. These results must be interpreted cautiously, for fat may be present in considerable amounts in cells (*e.g.* liver and many glandular tissues) without staining with osmic acid ; further, a solution of oleic acid and egg albumin can be prepared which does not stain with osmic acid. Many white corpuscles (lymphocytes) accumulate chiefly between the epithelial cells and their basement membrane, but also in the interstices between the cells. They take up fat, transport it through the reticulum of the villus into the central lacteal, where they disintegrate and liberate their contained fat.

From the *lacteals* the fat passes into the thoracic duct, and also to some extent directly into the *blood stream*. If the thoracic duct is ligated, fat absorption is diminished, but not entirely arrested ; there can thus be little doubt that fat passes directly into the blood under these conditions, and this probably takes place in the normal state too. Quantitative data concerning fat absorption are meagre because it is difficult to establish a permanent fistula of the thoracic duct in animals owing to it becoming rapidly blocked by coagulation of lymph. The classical observations of Munk were carried out on a girl with great swelling (elephantiasis) of one leg. Dilated lymphatics were visible under the skin and a fistulous opening was present below the knee which discharged clear lymph during a fasting period and milky fluid—identical with chyle—after a fat meal. Strange as it may seem, there was good evidence that most, if not all, of the chyle from the lacteals could be

collected from the fistula in the leg. Forty-one grams of lipanin (olive oil containing 6 per cent. free oleic acid) were administered ; during the following 13 hours 1134 grm. chyle were collected containing 25·1 grm. fat, so that *over 60 per cent.* of the ingested fat was recovered. Higher figures were never obtained ; some of the fat may have passed straight into the blood and, of course, there is no absolute proof that all the chyle escaped in the fistula in these experiments.

Blood-Fat.—The systemic blood-fat begins to rise one hour after a meal and reaches its maximum after six hours. The *neutral fat* from the thoracic duct enters the blood as finely divided particles about 1 μ in diameter. The details of the changes are as follows : (i) The amount of *fatty acids* in different combinations increases temporarily in both plasma and corpuscles, more perhaps in the latter than the former. (ii) The amount of phospholipine (" *lecithine* ") increases mainly in the red blood corpuscles ; the newly-formed phospholipine appears to be made from absorbed fatty acids, but the source of the necessary H_3PO_4 and the nitrogenous constituent (choline) is obscure ; what proportion of the absorbed fat is treated in this way in the red cells it is impossible to say, and it may be quite small. (iii) The amount of free *cholesterol* shows irregular changes ; it may increase slightly, depending on the amount which is available in the intestine from the food and bile. (iv) The amount of *cholesteride* (*i.e.* cholesterol united with fatty acid) increases chiefly in the red cells, probably as a result of the blood cholesterol uniting with absorbed fat (Leathes) (see Table).

DISTRIBUTION OF FAT IN THE *WHOLE* OF THE PLASMA AND CORPUSCLES OF DOG AFTER ADMINISTRATION OF 65 C.CM. OF OLIVE OIL.

(Data of Bloor, quoted after Leathes and Raper).

	In Corpuscles.		In Plasma.	
	Before Feeding.	Increase 4 hours later.	Before Feeding.	Increase 4 hours later.
As " lecithine " .	0·645 grm.	0·375 grm.	0·712 grm.	0·341 grm.
As cholesteride .	0·024 „	0·076 „	0·243 „	0·018 „
Glycerides, soaps .	2·221 „	2·582 „	1·071 „	0·419 „

After eight hours the lecithine of the corpuscles is almost down to the pre-feeding level.

But active absorption of fat may occur without the concentrations in the blood being appreciably altered. 60 grm. butter were given to eight normal men : in one case the blood-fat fell, in one it remained unchanged, and in six it rose ; the changes in blood cholesterol and lecithine bore no relationship to that of neutral fat.

The fat is probably removed from the blood by the liver, the tissues generally, and the fat depots. The blood-fat is also increased in the following conditions : (i) *Starvation* to a slight extent (p. 441) : (ii) *diabetes* (p. 419) ; (iii) *pregnancy* -the increase may be to the extent of 30 per cent., and is chiefly

due to a rise in the *cholesterol* esters (p. 393); there is also an accumulation of fat in the liver; (iv) *nephritis*; (v) *anæmia* (see Cholesterol p. 393).

Source of Depot Fat.—Adipose tissue consists to the extent of about 90 per cent. of fat, almost wholly triglyceride, which is derived from the fat of the food and fat synthesized in the body.

1. *Fat* of the food: if fat of known melting-point or of known iodine value is ingested, the fat deposited in the depots closely resembles it in these characters.

2. *Carbohydrate*: Young pigs fed on barley deposit large amounts of fat—more than could be derived from the fat and protein of the food even if it were assumed that all the carbon of the protein went to form fat, so the fat which had been deposited must have been partly derived from carbohydrate. Lusk has recently shown that *protein* may to some extent give rise to fat in dogs under exceptional circumstances; in view of the fact that some amino-acids are converted into glucose, there is no reason, chemically, why this sugar should not ultimately be turned into fat.

The stages of the transformation of sugar to fat may be as follows:

(1) *Glycerine*, $CH_2OH—CHOH\ CH_2OH$, can be readily formed from glyceric aldehyde, $CH_2OH—CHOH—CHO$, which in turn is readily derived from glucose.

(2) The origin of the necessary higher fatty acids is obscure.[1] Glucose can readily give rise to lactic acid (p. 354); this when warmed with a mineral acid yields acetaldehyde.

$$\underset{\text{lactic acid.}}{CH_3CHOH.COOH} \longrightarrow \underset{\text{acetaldehyde.}}{CH_3CHO} + \underset{\text{formic acid.}}{HCOOH}$$

(But this process has not yet been demonstrated *in vivo*; the necessary enzyme is present in yeast, but not in animal tissues). It is suggested that two molecules of acetaldehyde are condensed to form *aldol*, the process probably occurring in the liver.

$$CH_3CHO + HCH_2CHO \longrightarrow CH_3CHOH.CH_2CHO \text{ (aldol).}$$

Aldol was thought to proceed by oxidation directly to butyric acid, $CH_3CHOH.CH_2COOH$, but this has not yet been carried out *in vitro*. Butyric acid may perhaps be formed as follows:

$$\underset{\text{aldol}}{CH_3CHOH.CH_2CHO} \xrightarrow{-H_2O} \underset{\text{crotonaldehyde}}{CH_3CH=CH.CHO} \xrightarrow{+H_2} \underset{\text{butylaldehyde}}{CH_3CH_2CH_2CHO}$$

$$\xrightarrow[+O]{} \underset{\text{butyric acid.}}{CH_3CH_2CH_2COOH}$$

Further molecules of acetic aldehyde may then be condensed on to butyric acid to form 6, 8 and longer carbon chains until a 16 or 18 carbon chain is formed.

$$CH_3CHO + CH_3CH_2.CH_2COOH \longrightarrow CH_3CHOH.CH_2.CH_2CH_2COOH, \text{ etc.}$$

When carbohydrate is transformed into fat, a substance *rich* in oxygen is converted into one which is *poor* in oxygen. Much oxygen is left over in the body and less need be taken up from the atmosphere. The respiratory quotient, *i.e.* CO_2 evolved $/O_2$ absorbed, consequently rises above 1. When

[1] The liver may play a part in the reaction: if liver pulp is incubated at 37° C. for 24–48 hours there is a rise in the content of higher fatty acids, but the addition of glucose does not increase the process. (Leathes.)

fat is reconverted into carbohydrate, large amounts of oxygen are necessary for this chemical transformation over and above that necessary for the ordinary energy purposes of the body. The oxygen intake rises and the R.Q. falls.

These changes are well studied in the marmot, which deposits fat in the autumn when the R.Q. is high, *e.g.* 1·5 ; in the winter the quotient falls at times as low as 0·4—the animal lives on its stores of fat and is forming compounds richer in oxygen, probably glycogen and sugar (Pembrey).

Rôle of Liver.—The liver normally contains about 3 per cent. fat, with an iodine value of about 135 ; the fat of the adipose tissues has an iodine value of about 65. In certain conditions the fat content of the liver is increased—in diabetes, after pancreatectomy, and in poisoning with phloridzin or phosphorus ; it is found that as the amount of fat in the liver increases, so the iodine value falls, which suggests that fat is being *brought to the liver from the depots*. The liver fat may rise to seven times the normal under conditions in which the fat content of the other organs is hardly affected—this argues a special rôle for the liver in fat metabolism. The liver *desaturates fatty acids* : (i) if an unsaturated fat is administered, fat may be found in the liver which is more unsaturated still ; (ii) unsaturated acids containing up to *four* double linkages have been demonstrated in the liver. It is generally believed, but not proven, that H_3PO_4 and nitrogenous bases are also added to the fatty acids in the liver, to form phospholipines (lecithine-like bodies) which are then sent to the tissues. It is possible that desaturation may be preparatory to the final process of oxidation : the fatty acid may split at the double bond into a number of short fragments which then undergo oxidation at the β position (p. 431).

Fat of Tissues.—Fats form an integral part of the architecture of all cells and are as essential a constituent of protoplasm as protein ; they should not be regarded solely as reserves of energy. The total fat of the body can be divided into two parts : (i) *élément variable*, or *neutral fat*, which is used when needed for energy purposes ; (ii) *élément constant*, which cannot be reduced in amount without death resulting ; it persists during starvation and is uniform for all the individuals of a species. Starvation has practically no effect on the fat content of brain, kidney, lung, spleen, or heart—the fat here, is therefore almost entirely *élément constant* ; the fat in the muscles on the contrary is greatly diminished, showing that they are important storehouses of reserve fat ; fat may *accumulate* in the liver during starvation, but this is a transitory phenomenon which results from mobilization of fat from the reserves. Lecithine contains two molecules of fatty acid to one molecule H_3PO_4 ; the ratio of the molecular weights of fatty acid, H_3PO_4 is 18. In most organs a higher ratio is found, *e.g.* liver 36, kidney 24, pancreas 55 (man), indicating that fatty acids uncombined with phosphorus must also be present in the cells, *i.e.* as simple glycerides and cholesterol esters. Lecithine and cholesterol esters probably constitute the *élément constant*.

The fat present in healthy cells is incorporated in such an intimate manner with the rest of the " protoplasm " that it does not stain with osmic acid. If the cell is injured or poisoned, discrete fat globules appear which can be readily stained by stains for fat. The condition is called " *fatty degeneration*."

Utilization of Fat.—1. There is no evidence that skeletal muscle can use fat directly ; no consumption of fat can be detected in muscle tetanized

for some hours. Further, the modern work on muscular contraction seems to indicate that carbohydrate is the sole source of the energy of muscular activity. It is found, however, that on a diet of fat if exercise is prolonged the R.Q. of the excess metabolism is 0·7. This shows that fat is being used, but it is generally supposed that the fat is not used as such by muscle, but is first converted elsewhere into carbohydrate. According to Krogh, the mechanical efficiency is lower on a diet of fat than on one of carbohydrate, *e.g.* under 22 per cent. against over 24 per cent. in one series of experiments, presumably because the fat has first to be converted into carbohydrate and this process involves some loss of energy.

2. Fat may be directly utilized by the tissues. It is possible that fat must be present in the form of phospholipine before oxidation can commence ; but very little is known about the early stages of the process. It is possible that the fatty acid part of the molecule may first be broken at the double bond (introduced in the liver) into short chains which undergo oxidation. Light has been thrown on the details of the latter part of the process by the following experiments :

Benzoic acid (C_6H_5COOH) and phenyl-acetic acid ($C_6H_5CH_2COOH$) are very stable substances, and if ingested are excreted in the urine conjugated with glycine. If higher acids of this series are administered it can be shown that they lose *two* carbon atoms at a time, as shown by the products found (combined with glycine) in the urine. Thus the following reactions have been proved :

(i) $C_6H_5CH_2CH_2\overset{*}{C}H_2CH_2COOH \longrightarrow C_6H_5\overset{*}{C}H_2CH_2COOH \longrightarrow C_6H_5COOH$
phenyl-valeric acid — phenyl-propionic acid — benzoic acid

(ii) $C_6H_5CH_2\overset{*}{C}H_2CH_2COOH \longrightarrow C_6H_5CH_2COOH.$
phenyl-butyric acid — phenyl-acetic acid.

This suggests that oxidation to —COOH occurs at the *β carbon* (indicated by the asterisks above) and the two end carbon atoms are removed ; in support of this view is the formation of β hydroxy-butyric acid ($CH_3CHOH.CH_2COOH$) and aceto-acetic acid (CH_3COCH_2COOH) when fat combustion is incomplete, as in diabetes. β oxidation also occurs if the ammonium salt of butyric acid is incubated at 37° C. with H_2O_2 -aceto-acetic acid (and acetone) being formed.

Dakin administered phenyl-propionic acid and found a series of substances in the urine analogous to the acetone bodies of diabetes and all indicating that β oxidation takes place.

(i) $C_6H_5\overset{*}{C}H_2CH_2COOH$ (cf. butyric acid)

(ii) $C_6H_5\overset{*}{C}HOH.CH_2COOH$ (cf. β hydroxy-butyric acid) ; (iii) $C_6H_5\overset{*}{C}OCH_2COOH$ (cf. aceto-acetic acid) ; (iv) $C_6H_5\overset{*}{C}H=CH.COOH$

(v) $C_6H_5—COCH_3$ (cf. acetone)

It is undecided whether the β ketonic acid (iii. *sup.*) or the α-β unsaturated acid (iv. *sup.*) is first formed. The β hydroxy acid (ii) is derived secondarily from a reduction of (iii) or (iv).

The combustion of fats proceeds to completion, *i.e.* to CO_2 and H_2O, only if sugar is being burnt in adequate amounts at the same time ; if the sugar supplies are inadequate as in starvation, or if sugar is not properly utilized as in diabetes, the fats yield acetone bodies, *i.e.* β hydroxy-butyric and aceto-acetic acids. Carbohydrates are therefore called " anti-ketogenic " because they inhibit the formation of acetone bodies ; the glycerine (= 10 per cent.) of fat, and 58 per cent. of the protein which yield glucose in the body, act similarly. In addition to fat, certain amino-acids—leucine, tyrosine, phenyl-alanine, are also " ketogenic " and yield acetone bodies in the diabetic organism. No satisfactory explanation is forthcoming of the mechanism of the anti-ketogenic action of sugar. It is found that if the ratio of

$$\frac{\text{molecules of " ketogenic " substances}}{\text{molecules of " anti-ketogenic " substances}}$$

exceeds 2, acetone bodies acculumate. This is a point of practical importance in arranging the diet, particularly in diabetes ; the clinical rule given is that the fat content (F) of the diet must not exceed the sum of twice the carbohydrate (C) and half the protein (P)

$$F = 2C + \frac{P}{2}$$

The fat of the milk secreted by the mammary glands probably comes directly from the lecithine of the blood. This can be shown by comparing the lipoid content of the blood entering and leaving the mammary gland in cows during lactation (cf. p. 175).[1]

Rôle of Fat in the Diet.—1. Fats are an essential constituent of all cells especially in the form of phospholipine (lecithine) and cholesterol. These latter substances are present to some extent in the fat of the food or are synthetized from ingested neutral fat. Fat serves as a source of energy ; 1 grm. fat liberates 9·3 calories.

2. Fat can be readily stored, and thus constitutes the chief energy reserve of the body ; fat forms on an average about 12 per cent of the body weight, which is equivalent to 1100 C per kg.

3. The natural fats contain vitamins A and D, which are very important for health, growth, and ossification of bone.

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[1] Fat metabolism in biliary obstruction (see p. 392) and pancreatic disease (see p. 390).

PROTEIN METABOLISM

Digestion — Fate of amino-acids — Urea formation — Fate of non-nitrogenous residue—Essential amino-acids—End products of protein metabolism—Creatinine and creatine—Creatinuria—Uric acid metabolism—Blood uric acid—Gout —Starvation—Nitrogenous equilibrium—Protein in diet.

Digestion.—1. No digestion of protein occurs in the *mouth*.

2. *Stomach.*—i. The pepsin-HCl mixture acts on proteins converting them through the stages of acid metaprotein, primary and secondary proteoses to peptones. (ii) Caseinogen is converted by rennin into soluble casein. In the presence of calcium salts, insoluble calcium caseinate is precipitated, and is subsequently digested to the peptone stage. (iii) Nucleo-proteins have one molecule of protein split off leaving nuclein.

3. *Duodenum.*—i. Trypsin of pancreatic juice, acting in an alkaline medium, rapidly breaks down protein to alkali metaprotein, proteoses, peptone, polypeptides, and may liberate some amino-acids (*e.g.* leucine, tyrosine). Its digestive action is facilitated by the presence of bile-salts. In the body it is acting on protein which has already been partially digested by pepsin.

ii. Nuclein is further hydrolysed; another molecule of protein is split off and nucleic acid is liberated.

4. *Small Intestine.*—i. Erepsin of the succus entericus completes the breakdown of polypeptides to amino-acids; this occurs partly in the lumen and partly in the wall of the intestine.

(ii) Nucleic acid is acted on by a series of ferments which are present in the lumen, or can be extracted from the mucosa, of the small intestine. (*a*) It is first split up into its four constituent *mononucleotides*, each of which consists of H_3PO_4, carbohydrate (hexose or pentose), and base (purine or pyrimidine bases). (*b*) H_3PO_4 is then split off, leaving combinations of sugar and base called *nucleosides*. The two pyrimidine nucleosides are not further disintegrated. (*c*) The two purine nucleosides are further split up into carbohydrate and purine bases, namely *adenine* (6 amino-purine) and *guanine* (2 amino-, 6 oxy-purine).

Nucleic Acid Nucleoside

Mononucleotide = H_3PO_4— | Carbohydrate—Base | (Adenine)

H_3PO_4—Carbohydrate—Base

H_3PO_4—Carbohydrate—Base

H_3PO_4—Carbohydrate—Base (Guanine).

Fate of Amino-Acids.—The amino-acids form the end products of protein digestion. They are absorbed from the intestine into the portal radicles and conveyed to the liver. (i) A proportion pass through the liver into the systemic circulation, from which they are taken up by the tissues and built up into their substance to make up for the wear and tear which occurs during activity. The level of the systemic amino-acid is 3 to 5 mg. per 100 c.cm. After a protein meal it may rise to 6 mg.; (ii) The rest of the amino-acids undergo a process of *deamination* in the liver; NH_3

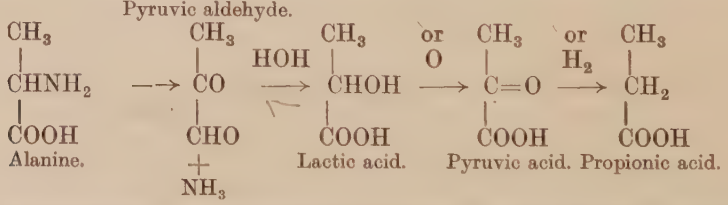
is liberated and a non-nitrogenous residue is left ; the NH_3 is converted in the liver into urea.

i. If an animal is starved for 24 hours to create nitrogen want[1] in the tissues and 12 grm. of alanine (CH_3CHNH_2COOH) are injected intravenously, it is found that only 1·5 grms. remain in the circulation after 5 minutes. The amino-acid content of the various organs is determined before and after the injection. It is found that all the tissues, *e.g.* muscle, kidney, take up amino-acid which they retain, presumably for tissue repair. The liver is especially greedy and takes up more amino-acid than the other tissues. It does not retain it long, however, because the amino-acids are rapidly deaminized. The NH_3 is converted into *urea* which is passed into the systemic circulation. The liver amino-acid content falls as the blood urea rises.

(ii) The work of Mann (p. 399) proves conclusively that (in the dog) *urea formation is carried out solely in the liver.* If the liver is extirpated no fresh urea is formed ; the blood urea steadily falls if renal secretion continues, but if anuria is present, the blood urea is maintained at a constant level.

(iii) Certain older experiments must be reconsidered in the light of these observations. The blood supply to the liver may be considerably reduced by anastomosing the portal vein to the inferior vena cava and tying the portal vein above (Eck's fistula), thus shunting the portal blood directly into the systemic circulation. The functional activity of the liver is diminished but by no means ceases (cf. p. 400). The animal may live for a considerable time in good health on a diet consisting mainly of carbohydrate, but on a high protein diet it becomes ill, and convulsions and coma develop. Urea formation is greatly diminished, but still continues to some extent owing to the amount of liver tissue which is still active.

Deamination is probably a simple process which involves little loss of energy (only 5 to 20 per cent.). The nitrogenous fraction of the amino-acid is thrown off, so that the valuable non-nitrogenous portion may subsequently be utilized. Dudley and Dakin have shown that α amino-acids in solution in water undergo spontaneous dissociation into α ketonic aldehydes and NH_3. This reaction is probably accelerated in the body by an enzyme : alanine, for example, is converted into NH_3 and pyruvic aldehyde, which may then undergo hydrolysis to lactic acid, oxidation to pyruvic acid, or reduction to propionic acid.



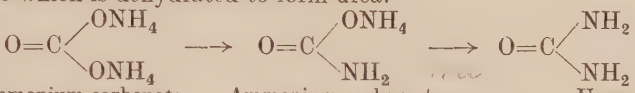
It must be recalled, however, that Mann found that *deamination practically ceased after hepatectomy* (p. 399).

The process of deamination is probably *reversible.* Given the appropriate fatty acid grouping the tissues can take up NH_3 and re-form amino-acids. Thus if lactic or pyruvic acids are perfused through the liver alanine is formed.

[1] In Mann's experiments (p. 399), which were carried out on *normal* (not *starved*) animals, amino-acid was not retained in the tissues.

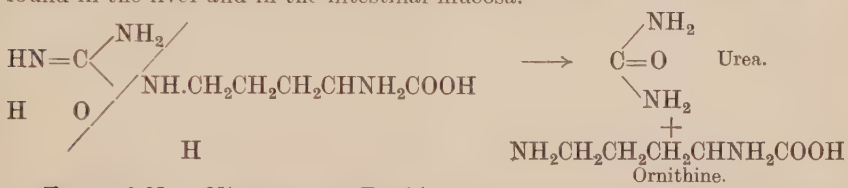
The NH_3 formed is first seized on by the strong acid radicles and converted into ammonium salts and excreted in the urine as such. The amount of NH_3 thus utilized depends (p. 225) on the reaction of the blood. In acidæmia there is a relative excess of fixed acid radicles and more NH_3 is used to neutralize them; in alkalæmia there is a relative excess of the fixed base of the blood to deal with acid radicles and so less NH_3 is used.

The rest of the NH_3 unites with the weak carbonic acid, to form ammonium carbonate which is dehydrated to form urea.[1]



Ammonium carbonate — Ammonium carbamate. — Urea.

Ammonium carbonate or carbamate when perfused through the liver give rise as expected to urea. Small amounts of urea may be formed from arginine (Δ guanidine amino-valerianic acid) by a ferment arginase which is found in the liver and in the intestinal mucosa.



Urea.

Ornithine.

Fate of Non-Nitrogenous Residue.—As already shown (p. 420), in the diabetic 58 per cent. of the carbon of the ingested protein is converted by the liver into glucose. In the normal body this fraction is believed to be treated similarly and helps to maintain the sugar of the blood; it is not readily stored as glycogen. Some of the residues give rise to acetone bodies in the diabetic and so perhaps go "the way of fat metabolism" normally. The fate of the individual amino-acids has been carefully studied in the diabetic animal. Glycine ($CH_2.NH_2.COOH$), alanine ($CH_3.CHNH_2.COOH$), serine ($CH_2OH.CHNH_2.COOH$) and cystein ($CH_2SH.CHNH_2.COOH$) are converted wholly into glucose; aspartic acid ($COOH.CH_2.CHNH_2.COOH$), glutamic acid ($COOH.CH_2.CH_2.CHNH_2.COOH$), arginine, and proline give rise to sugar to the extent of *three* of their carbon atoms only; in addition valine ($CH_3.CH_3$ \ $CH.CHNH_2.COOH$), isoleucine, and oxyproline may also form sugar to some extent. Leucine $CH_3.CH_3$ \ $CH.CH_2.CHNH_2.COOH$

phenyl alanine $CH_2.CHNH_2.COOH$ and tyrosine $CH_2.CHNH_2.COOH$.

yield *acetone* bodies; histidine and tryptophane yield neither sugar nor ace-

[1] According to Werner, urea has a cyclic formula and is formed from ammonium cyanate ($NH_4OC{=}N$).

tone bodies. Glycine and cystein are used in the formation of the bile-salts, the cystein being converted into taurine

$$\underset{\text{Cystein}}{CH_2SH.CHNH_2.COOH} \longrightarrow \underset{\quad|\quad}{CH_2SH} \quad \underset{\quad|\quad}{CH_2NH_2} + CO_2 \qquad \longrightarrow \underset{\quad|\quad}{CH_2.SO_2.OH} \quad \underset{\text{Taurine.}}{CH_2NH_2}$$

Essential Amino-Acids.—We have noted (p. 434) that the body can probably synthesize amino-acids if the appropriate fatty groupings are provided. The simpler amino-acids, *e.g.* glycine (amino-acetic acid) or alanine (amino-propionic acid) can readily be formed from NH_3 and the products of carbohydrate metabolism. Certain of the amino-acids must be provided in the protein of the food if normal health and growth are to be maintained. *Tryptophane* (α amino-β indole-propionic acid) is essential for maintenance of body weight; *lysine* is essential for growth. *Tyrosine* is very important, for adrenaline and thyroxine are probably derived from it. It may be omitted from the diet without harm if the other aromatic amino-acids are provided. Growth takes place more rapidly if adequate amounts of *cystine* are provided, as it is necessary to form glutathione (p. 364). Histidine is essential too (Rose).

If a basal ration of protein-free milk (which contains the necessary salts and vitamins), carbohydrate, and fat be given to rats, the biological value of different proteins can be determined by adding them in turn to the diet. Liberal amounts of lactalbumin, ovalbumin (eggs), glutein (wheat), glutelin (maize), excelsin (brazil-nut) give a normal growth curve. Casein is deficient in cystine, and must be given in large amounts or together with lactalbumin to obtain good growth. Gliadin of wheat contains no lysine, and so no growth takes place. Zein of maize is deficient in both tryptophane and lysine, so that weight is steadily lost if it is the sole protein of the diet.

Specific Dynamic Action of Protein.—The ingestion of protein stimulates the metabolism for about three hours to the extent of about 20 per cent. Carbohydrate and fats have a much slighter stimulant action. It is believed that the amino-acids resulting from protein digestion can stimulate cellular activity (cf. p. 320).

End Products of Protein Metabolism.—The well-known table (after Folin) illustrates the difference in the composition of the urine on a diet rich or poor in protein (but of adequate caloric value).

	Protein Rich Diet.	Protein Poor Diet.	
Volume of urine .	1170 c.cm.	385 c.cm.	Greatly reduced.
Total nitrogen . .	16·8 grms.	3·6 grms.	,,
Urea nitrogen . .	14·7 ,, =87 %	2·2 ,, =61·7 %	,,
Uric acid nitrogen .	0·18 ,,	0·09 ,,	Halved.
Ammonia nitrogen .	0·49 ,,	0·42 ,,	Unchanged.
Creatinine nitrogen .	0·58 ,,	0·6 ,,	,,
Inorganic SO_4 . .	3·27 grms. =90 %	0·46 grms.	Greatly reduced.
Ethereal SO_4 . .	0·19 ,,	0·10 ,,	
Neutral sulphur. .	0·18 ,,	0·20 ,,	Unchanged.

The table throws much light on the origin of the different urinary constituents. It is clear that the total nitrogen excretion in the urine runs parallel

with the protein intake. On diets of adequate caloric value but very low in nitrogen, the nitrogenous output may be reduced, *e.g.* from 16·8 grms. to 3·6 grms. **Urea** is the chief nitrogenous constituent of the urine, and is an index of protein intake; but even on a low protein diet it forms 61·7 per cent. of the urinary nitrogen, though the total amount is much diminished. After a protein meal all the ingested nitrogen is eliminated in the urine as additional urea within 6 to 8 hours. Urea is still the chief nitrogenous constituent of the urine in starvation, but it is then coming from tissue protein which is used for energy purposes. On an average mixed diet about 30 grms. urea are excreted daily. The *ammonia* excretion is not dependent on the nitrogenous intake, but on the reaction of the blood (p. 224). Creatinine is independent of the diet. Uric acid is reduced by one-half on a protein poor diet, suggesting that half is derived from the food and half from tissue activity.

The metabolism of ingested food is called *exogenous*; that of the tissues themselves is called *endogenous*. Urea and half the uric acid excreted are an index of exogenous metabolism or nitrogenous intake; creatinine and half the uric acid are an index of endogenous metabolism or tissue activity.

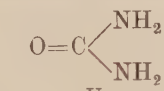
The *sulphur* contained in the cystine of the food is probably removed in the liver and oxidized to sulphuric acid. It is then neutralized by base (Na, K), and excreted in the urine as inorganic sulphate. This, like urea, depends on the protein intake, and is exogenous in origin.

Some of the aromatic amino-acids—tryptophane and tyrosine—pass into the large intestine where they undergo putrefactive change and are converted into indol, skatol, and phenol. These substances are absorbed into the blood, carried to the liver, oxidized to indoxyl and skatoxyl, etc., conjugated with sulphate, and excreted in the urine as the so-called *ethereal* sulphates. Indoxyl potassium sulphate is referred to as *indican*. The ethereal sulphate of the urine is said to be an index of *intestinal* putrefaction (see discussion, p. 412).

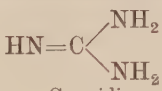
By *neutral* sulphur is meant unoxidized sulphur compounds like cystine, mercaptan, etc. Its excretion in the urine is unaffected by the diet, and, like creatinine, it represents endogenous metabolism.

Creatinine and uric acid metabolism merit fuller consideration.

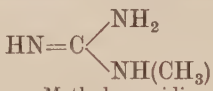
Creatinine.—The following chemical relationships will be recalled:



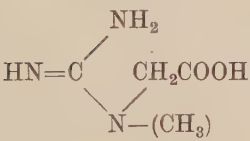
Urea.



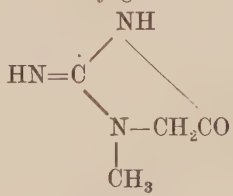
Guanidine.



Methyl guanidine.



Creatine.
Methyl guanidine.
Acetic acid.



Creatinine
(Anhydride of creatine),
i.e. 1 molecule H_2O less.

Creatine and creatinine are readily transformed into one another, especially in alkaline media.

1. *Creatine* is found (i) mainly (98 per cent.) in striated muscle ; (ii) to a slight extent in brain, heart muscle, and testis. It is probably present in the uterus, especially when in the gravid state.

The creatine content of striated muscle rises steadily during fœtal and post-natal growth till the maximum level of the adult is attained. The *origin* of creatine is highly speculative. It has been suggested that it is a detoxication product of guanidine or methyl guanidine (cf. p. 159).

2. *Creatinine* is found in the urine and in minute amounts in the blood and tissues. It is a waste product, and is regarded as derived from endogenous metabolism only, probably from the creatine of muscle.

Evidence.—(i) If creatinine is administered by the mouth, it is promptly excreted up to 80 per cent. of the amount ingested ; none of it is broken down to NH_3 or urea. (ii) The daily output of creatinine is constant and is entirely independent of the protein intake or the total amount of nitrogen excreted. There may be lessened excretion at *night*. (iii) The creatinine output is related to muscle bulk and efficiency, and is higher in muscular and athletic individuals. (iv) (*a*) If creatine is ingested up to 1 grm. daily, none of it appears in the urine ; it is probably stored in the muscles as such. (*b*) Up to 5 grm. daily, a proportion of the creatine is stored, and some is excreted as such. (*c*) If 20 grms. of creatine are ingested, 15 grms. are excreted as such, 4·5 grms. are retained, and 0·5 grm. is excreted as *creatinine* in the urine.

It is therefore suggested that creatinine is derived from the metabolism of muscle, and that its precursor is creatine or some complex body containing creatine. Recently a *creatine-phosphate* compound ("*phosphagen*") has been demonstrated in muscle which is broken down and then resynthesized during muscular activity (p. 355). The output of creatinine during a period of work is invariably greater than during the corresponding time of a day of inactivity. This is, however, immediately followed up by a period of unusually low output, so that the twenty-four hour output is unaffected by work.

Blood Creatinine.—Values for creatinine above 1 to 2 mgrms. per 100 c.cm. blood probably indicate a pathological condition of the kidneys, because its level in the blood is normally kept very constant. Figures of 3 to 5 mgrms. indicate considerable *renal damage*, while concentrations above 5 mgrms. frequently indicate an early fatal termination (cf. p. 474).

Creatinuria.—Creatine may appear in the urine under the following conditions :

1. i. It is constantly and normally present in children of both sexes up to the age of puberty. This fact may be associated with the low storage power of the muscles for creatine at any early age.

ii. It is found in an intermittent manner in the urine of women, but is said not to be related to menstruation. There is a continuous creatine excretion during pregnancy. It rises to a maximum of 1·5 grms. daily after delivery, when it may be derived from the involuting uterus.

Creatine is not excreted by normal men.

2. In certain pathological states of muscle, *e.g.* the group of *myopathies*, creatine is excreted, because of the low storage power of the muscles. Even if only small amounts of creatine are ingested, 90 per cent. or more appears unchanged in the urine.

3. In any condition in which unusual breakdown of the tissues, especially the muscles, occurs, *e.g.* in starvation, diabetes, exophthalmic goitre, and

fever (from the increased metabolic rate), creatine is excreted. In all states of under-nutrition the muscles bear the brunt of the burden. As their substance is broken down for energy purposes, creatine is liberated, some of which is stored in the muscles which are still intact, and the rest is passed out in the urine.

Uric Acid.—1. Exogenous Uric Acid.—This is derived from the nucleo-proteins and other *purine*-containing bodies of the food.

i. Nucleo-proteins are present in all food-stuffs which are rich in nuclei, *e.g.* liver, pancreas, kidney, brain, yeast. The digestion of these substances in the intestine was described on p. 433. The products formed—namely, H_3PO_4, carbohydrate (hexose or pentose), pyrimidine nucleosides (carbohydrate in combination with pyrimidine base), and two purine bases, adenine and guanine—are absorbed into the portal circulation.

ii. Purine bases, *e.g.* xanthine and hypoxanthine in meat extracts, soup, beef tea, etc.

iii. Methyl purines—theophylline, caffeine, theobromine—present in tea, coffee, and cocoa.

In the tissues and perhaps particularly in the liver, adenine (6 amino-purine) and guanine (2 amino- 6 oxy-purine) are de-aminized to hypo-xanthine (6 oxy-purine) and xanthine (2, 6 dioxy-purine) respectively.

Hypoxanthine is oxidized to xanthine, and the latter to uric acid (2, 6, 8 trioxy-purine). The fate of the pyrimidine bases is unknown.

2. Endogenous Uric Acid.—All the organs of the body contain enzymes which can break down the nucleo-proteins of the tissue nuclei through the stages already described to form uric acid.

3. Excretion.—Uric acid is excreted chiefly as the mono-urate. The total output depends on the purine content of the diet, but is about 0·75 to 1 grm. daily on an average. On a purine-free diet it falls to about one-half, *i.e.* 0·3 to 0·5 grm., but the amount varies widely in different individuals, and is influenced by the other constituents of the diet. (i)*Protein* ingestion stimulates the uric acid output: thus changing from a diet of milk and eggs to one of starch and cream lowers the uric acid excretion, though both diets are purine free. Amino-acids even in small amounts have a similar action. Glycine, alanine, glutamic and aspartic acid increase the hourly fasting output of uric acid, probably by stimulating cellular metabolism (cf. p. 320). (ii) The *caloric* value of the diet is important. On a constant protein intake, raising the caloric value of the food increases the uric acid output. (iii) If the addition to the food consists mainly of carbohydrate and little fat, there is increased uric acid excretion. If the diet consists of little carbohydrate and much fat, the uric output is small (Graham and Poulton). It is suggested that *carbohydrate* may be converted in the body in some unknown way into purine bodies.

The practical points are these: to diminish uric acid formation, the diet should have a *low purine* content, a *low protein* content, a *low calorific value*, and consist rather of *fat* than of carbohydrate.

The endogenous uric acid excretion is less by night than by day. Moderate exertion has little effect, but strenuous exercise increases the output. As already pointed out, endogenous uric acid is to some extent related to tissue activity.

Synthesis of Purine.—Purine can undoubtedly be synthesized by the

body. The growing child on a milk diet, which is almost purine free, puts on weight and increases the number of its nuclei and its purine content. A Dalmatian dog, fed for a year on a purine-free diet, excreted 100 grms. of uric acid,[1] of which no more than 10 grms. could have come from the preformed purine of the tissues (Benedict).

The mechanism of purine synthesis is unknown. Ackroyd and Hopkins found that purine cannot be synthesized if the diet is deficient in *either* of the two amino-acids, arginine and histidine, but the reason for this is not clear.

Blood Uric Acid.—The normal limits are 0·7 to 3·7 mgrms. per cent., with an average of 2 mgrms. per cent. (Folin). It is raised in *gout* up to 9 mgrms. per cent. Ingestion of purine-containing food has no effect on the blood uric acid in normal people, but raises it in cases of *renal insufficiency*. It is claimed that the uric acid is the first nitrogenous constituent to be retained in nephritis, values of 6 mgrms. or over occurring before the other nitrogenous constituents are increased. In *uræmia*, figures as high as 27 mgrms. may be obtained. In *leukæmia* and *pneumonia* considerable breakdown of nuclei of white blood corpuscles is occurring, and the blood uric acid is raised. The kidneys are excreting a great deal of uric acid, but are unable to eliminate it as rapidly as it is formed.

The way in which uric acid is carried in the blood is still unsettled. It is suggested that part of it may be carried in a colloidal form. Benedict claims that in the red blood corpuscles of the ox and man, uric acid is present combined with d-ribose (a pentose found in yeast nucleic acid), in relatively large amounts as compared with the free uric acid usually estimated. Uric acid is liberated from this combination with the sugar, by hydrolysis with HCl, or by the enzymes present in blood when it is allowed to stand aseptically for some days. This combined uric acid does not react with the reagents employed in Benedict's colorimetric estimation.

Gout.—Gout is a chronic disorder characterized by an excess of uric acid in the blood, by a deposition of mono-sodium urate in the cartilages of the joints and in other structures, and by recurring attacks of acute arthritis.

The cause of the excessive concentration of uric acid in the blood of gouty patients is unknown. There is no evidence of over-production of purine bodies, so that the defect may be one of elimination, or failure of disposal of uric acid in the body. It has been suggested that there is failure of the kidneys to excrete uric acid adequately, although they eliminate the other nitrogenous constituents of the blood, *e.g.* urea, in a normal manner. Possibly uric acid is circulating in the blood in some *abnormal* combination, which prevents its filtration by the glomeruli of the kidney.

No satisfactory explanation is available to account for the deposition of urates in the cartilages of the joints. The blood uric acid is raised to considerably higher levels in some cases of chronic nephritis and leukæmia without such deposition taking place.

The cause of the arthritis in acute gout is also obscure. It is generally assumed that the inflammation is excited mechanically by the deposition of urate crystals in the tissues. Uratic concretions may, however, attain a large size without causing any symptoms whatever.

The excretion of uric acid in the urine is reduced just before an attack,

[1] The Dalmatian dog excretes uric acid and does not convert it into allantoin.

and is increased during the attack. Between the attacks it may be about normal or slightly diminished.

Salicylates and *atophan* greatly increase the urinary uric acid excretion and lower the blood concentration in gout. Graham has shown that much of the uric acid eliminated under the influence of atophan is actually drained out of the tissues and the tissue fluids. The increased elimination ceases after two days, and further use of the drug fails to decrease further the blood uric acid.

The dietetic measures recommended to diminish uric acid formation are summarized above (p. 439).

Starvation.—During starvation, the subject must live on his own tissues for energy purposes. During the first two days the glycogen stores of the liver are used up. For the greater period of the fast, the tissues are used ; a minimum of protein and much more fat are employed. When the fat stores are exhausted, protein alone is available, and death rapidly results.

Nitrogenous excretion falls during the first week to a minimum. The amount excreted is greater if the diet had previously contained much protein. After the seventh day the minimum level of nitrogen loss is reached, and is maintained till just before the end, when it rises steeply (" premortal rise ").

In the normal adult the amount of nitrogen eliminated from the body (almost entirely in the urine) is equal to the amount ingested. During starvation very extensive nitrogenous loss occurs. 1 grm. of nitrogen in the urine represents the breakdown of 6·25 grms. protein. A starving man on the fifth day of his fast, when his energy output was 2000 C., excreted 11·4 grms. N. This was derived from the burning of 71·5 grms. of tissue protein, which yielded roughly 300 calories (1 grm. protein = 4·1 C.). The rest of the energy, *i.e.* 1700 calories, must have been derived from about 190 grms. of fat (1 grm. fat = 9·3 C.). The fasting body was using protein and fat in the proportion of 71·5 : 190, *i.e.* about 1 : 2·5

The metabolic rate is diminished, *e.g.*, from 960 calories per sq. metre daily, to 737 calories on the thirty-first day of the fast, with corresponding diminution of the oxygen consumption and the CO_2 output.

Owing to lack of carbohydrate, the combustion of fats is incomplete and stops short at β oxy-butyric and aceto-acetic acid, which appear in the urine. The usual steps are taken to compensate for the tendency to acidæmia, *i.e.* increased pulmonary ventilation and fall of alveolar CO_2 tension ; increased acidity of the urine ; increased NH_4 excretion. As the depot fat is mobilized, there is a slight rise in the blood-fat and fatty infiltration of the liver takes place. The blood sugar falls slightly, and then is maintained at a steady level. It is probably formed from protein in the liver (if hepatectomy is performed, hypoglycæmia results).

Creatine appears in the urine (p. 438). The creatinine excretion in the urine falls as the muscle bulk is diminished.

The brain and heart lose only 3 per cent. of their bulk. The muscles, liver, and spleen lose 31 per cent., 54 per cent., and 67 per cent. respectively. The essential organs are thus spared as far as possible

Death occurs after about four weeks, when the body weight is reduced by 50 per cent. The temperature only falls just before the end.

Nitrogenous equilibrium can be maintained on a diet of protein alone if protein is administered in sufficient quantity to supply the *full energy requirements* of the body. This can be readily done in carnivorous animals, but

only exceptionally in the human subject. Thus in the case of the man mentioned above whose fasting requirements were 2000 C., the ingestion of protein will raise the energy output further. Meat contains about 20 per cent. protein, each 1 lb. (500 grms. approximately) yielding 400 calories, so that about 6 lb. would have to be consumed daily to provide the energy needs in this subject at rest, and considerably more would be necessary during exercise. Eskimos are said to consume about 8 lb. meat a day (p. 412), but such quantities are greater than the normal human alimentary canal can cope with. If an amount of protein is given to a *starving* person equivalent to the amount of tissue protein undergoing destruction, there is an almost equivalent increase in the nitrogenous excretion in the urine ; the administration of 71·5 grms. protein as food only supplies 300 calories and the body still needs another 1700 calories. So long as the *full energy requirements* of the body are not met by the food ingested, the tissues are broken down ; tissue protein and fat are used in the proportions noted above, and nitrogenous loss continues.

If carbohydrate and fat are added to provide energy, much less protein is necessary to produce nitrogenous balance. These substances—especially carbohydrate—are termed *protein-sparers*. By giving enough carbohydrate to a fasting person it is possible to lower the N excretion to one-third its previous level. Similarly, the daily N excretion of 16 grms. on an ordinary diet can be reduced to 6 grms. or less (*e.g.* 3·6 grms., p. 436), by giving adequate supplies of carbohydrate and reducing the protein consumption. But even if unlimited amounts of carbohydrate and fat are given, it is found that certain minimum amounts of protein are necessary to maintain N balance. This *irreducible protein minimum* varies with the kind of protein given. The relative values probably depend on the amount of the essential amino-acids contained in these proteins. It is impossible to maintain N equilibrium on diets which are deficient in the essential amino-acids, no matter how much protein is consumed, *e.g.* if gelatin[1] or zein (p. 436) are the sole source of protein.

100 grms. protein are usually recommended in the diet. If the right proteins are used nitrogenous equilibrium can be maintained on considerably less, but a bigger protein ration allows a factor of safety should proteins of lower biological value be used, and ensures that adequate amounts of the essential amino-acids which are so important for bodily welfare be ingested.

Nitrogen can be *retained* in the body : (i) During growth ; (ii) after recovery from wasting diseases ; (iii) by overfeeding an animal with protein. The cat may double the weight of its muscle bulk on a high protein diet. In the case of man, however, increased ingestion of protein merely results in increased nitrogenous excretion.

Rôle of Protein in the Diet.—1. It is the sole source of the nitrogen and sulphur which are needed for tissue repair. It provides the amino-acids which are used for the manufacture of certain essential secretions and enzymes (cf. pp. 436, 455).

2. It is a source of energy, each 1 grm. protein yielding 4·1 calories in the body.[2]

3. It stimulates the metabolic activities of the body.

[1] Gelatin is deficient in both tryptophane and tyrosine.

[2] When combusted in a bomb calorimeter each gramme of protein yields 5·6 C. ; but in the body the combustion of protein is not so complete, for some of the end products which are excreted in the urine are still capable of further oxidation.

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THE VITAMINS

Vitamin A—Vitamin B—Beri-beri—Pellagra-preventing (P-P) factor—Vitamin C—Scurvy—Vitamin D—Rickets—Radiant energy—Osteomalacia—Calcium and phosphorus metabolism—Vitamin E—Rôle of pigments of food—Nutritional œdema—Essentials of diet—Energy requirements—Under-nutrition—Composition of foodstuffs—Rôle of different constituents.

THE vitamins are substances the presence of which in the food is essential for normal health and growth. The chemical composition of most of the vitamins is not yet clearly established.

Vitamin A (Fat-Soluble A).—SOURCE.—It is found in *fats* of animal origin, *e.g.* milk, butter, cream, beef-fat, cod-liver oil; it is stored in considerable amounts in the *liver* fat of many animals; it is present in eggs and the embryo of seeds; and in green vegetables. It is absent from root vegetables and from the vegetable fats, *e.g.* olive oil, linseed oil, coco-nut oil; it is consequently absent from purely vegetable margarines. It is not found to any extent in lard.

It is believed to be primarily synthesized in the leaves and seeds of plants. Simple processes like pressure fail to remove the vitamin A found in seeds, and this accounts for its absence from vegetable oils. The vitamin content in fats of animal origin depends on the amount of vitamin present in the animal's food during life.

PROPERTIES.—i. It is readily extracted from the fats, in which it is found, by the ordinary fat solvents; *e.g.* alcohol, ether, benzene.

ii. Partially successful attempts have been made to isolate vitamin A from cod-liver oil. On treatment with hot alcoholic caustic potash 99 per cent. of the weight of the oil is converted into soap (indicating that it consisted originally of neutral fat); this fraction is inactive. One per cent. by weight is not saponified by this treatment, and this part contains all the active material. Half of this consists of inactive cholesterol which can be precipitated with digitonin. The remaining fraction containing the vitamin is distilled *in vacuo* at a temperature of 180° to 200° C., and highly active material is obtained, $_2\frac{1}{00}$ mgrm. of which given daily can keep a rat alive when added to the diet. Vitamin A is thus a fairly stable substance which can resist saponification and distillation at 200° C. (Drummond); but it is readily destroyed by *oxidation* or by exposure to *sunlight* (Peacock and Wright).

EFFECT OF ABSENCE FROM DIET.—A synthetic diet consisting of pure caseinogen, pure wheaten starch, olive oil, a mixture of inorganic salts, yeast, and orange juice, is complete in all respects except for the absence of vitamin A. Young rats fed on such a diet grow for a short time and then cease to put on weight, and gradually go downhill. Fully grown animals may survive for months, but finally succumb to some intercurrent infection.

Pathologically, striking changes are found in the eyes, the intestine, and the respiratory tract.

i. *Eyes.*—The lachrymal glands cease to produce tears; the outer layer of the cornea undergo necrosis; inflammatory processes occur in the con junctiva and may involve the anterior and posterior chambers of the eye leading to complete blindness. The eye disorder is referred to as *xeroph thalmia*, and is a specific sign of vitamin A deficiency.

ii. *Alimentary Canal.*—The cells of the salivary glands are not functionin and appear shrunken; the epithelium of the ducts is proliferated and the lume is partially occluded. The mucus-secreting cells of the intestine are atrophie and the tips of the villi are necrosed; masses of bacteria are found filling th lumen of the glands.

iii. The upper *respiratory tract*, particularly the nasal passages, trachea and bronchi shows a transformation of the lining epithelium into a stratifie epithelium of flattened cells which undergo extensive keratinization. Simila changes are seen in the vagina (p. 452). It is suggested that in the absence o vitamin A the nutrition of these regions suffers, and their local resistance t infection is reduced. From these enfeebled sites, organisms may pass int the blood stream. The blood platelets are found to be diminished in numbe (*thrombopenia*). It is thought they are playing a defensive part, attachin themselves to the invading bacteria and clumping them. Ultimately th weakened areas are overcome, and broncho-pneumonia, enteritis, and in flammation of the eyes may develop and prove fatal.

In mice fed on a diet deficient in vitamin A, the introduction of suitabl measured doses of mouse-typhoid bacilli gave a mortality rate of 80 to 100 pe cent. When the experiment was repeated on mice fed on the same diet bu with the addition of large amounts of vitamin A, the mortality rate was onl 10 to 20 per cent., though in all external appearances the two batches of mic appeared equally normal. In Denmark, during the war, when the fats rich in vitamin A were exported, and the populace lived largely on margarine an skimmed milk, several outbreaks of xerophthalmia and broncho-pneumonia were reported. Mori has described 1500 cases of xerophthalmia in Japanes children fed on inadequate diets and found that the condition was cured b the administration of cod-liver oil.

It is important to remember that a supply of vitamin A which is sufficien for growth and for apparently normal health may be insufficient to meet th added demands of pregnancy and lactation. The content of vitamin A i lung tissue varies directly with the amount in the ingested food, and it is pos sible that deficiency of this vitamin may predispose to the development o pulmonary tuberculosis and other lung diseases in man. It is significant tha cod-liver oil, which is very rich in vitamin A, has been long recognized as of grea value in these conditions. As milk is such an important source of the vitamin it should form an integral constituent of the diet, especially of children.

Summary.—Vitamin A is necessary for the proper growth and health o young animals. Its action may be to stimulate the resistance of certain areas—*e.g.* intestine, lungs, eyes—against infection.

Vitamin B.[1]—It is probable that the substance hitherto designated " vitamin B " consists of two or more substances: one that is necessary fo

[1] It is suggested that the anti-neuritic factor be called vitamin F (after Funk who contributed notably to this subject) and the P-P factor, vitamin G (after Goldberger whose studies are described above); the term " vitamin B " may be retained to describe the mixture of these substances.

growth and normal *intestinal activity* in young rats ; the same or possibly a distinct substance prevents *beri-beri* in pigeons and man (anti-neuritic factor) ; a substance of slightly different distribution is related to the prevention of *pellagra* (P-P factor).

Sources.—It is found in most natural food-stuffs, especially in *seeds* and *eggs*. In the pulses (pea, bean, lentil) it is distributed throughout the seed ; in the cereals it is only found in the germ and the bran. It is found in *yeast* and in commercial extracts of this substance ; and to some extent in meat.

Properties.- -" Vitamin B " is only soluble in water, aqueous alcohol, and glacial acetic acid. It is stable at high temperature in acid solution, but is rapidly destroyed by alkali (cf. p. 447). " Vitamin B " is present in bread in amounts which vary directly with the proportion of wheat *germ* used in preparing the flour.

Effect of Absence from Diet.—Young rats fed on the synthetic diet described above, but with vitamin A added (cod-liver oil) and yeast omitted, immediately stop growing. There is a fall of temperature, loss of appetite, and progressive atrophy of the lymphoid tissues throughout the body which results in a progressive diminution in the number of circulating lymphocytes (lymphopenia) and defective absorption of fat from the intestine. There is delayed passage of the food along the alimentary canal, and putrefaction of the retained food-stuffs. Possibly absorption of toxins may occur through the unhealthy mucous membrane. The bactericidal power of the blood is diminished, possibly because of the subnormal temperature. The administration of vitamin B rapidly leads to the disappearance of these symptoms. If the condition is allowed to progress, the animal becomes gravely emaciated, and dies practically of inanition.

It is suggested that one of the factors present in " vitamin B " exerts a specific stimulating action on the functions of the digestive tract, enabling effective digestion and absorption of the food to occur.

Beri-beri. — Beri-beri occurs in the rice-eating population of Japan, Malay Peninsula, etc. It is only found in people living almost exclusively on so-called " polished " rice from which the germ and husk have been removed by milling. It must be remembered, however, that polished rice is deficient in *all* the vitamins, in mineral salts, in proteins, and in fats, so that the resulting symptoms cannot be attributed to vitamin B deficiency alone. The symptoms can be understood from a consideration of the pathological findings. The heart is flabby and shows fatty degeneration ; there is evidence of failure of the circulation. Inflammatory lesions are present in the stomach and duodenum. Degeneration is found in the peripheral nerves, in the vagus, and in the central nervous system, especially in the anterior horn cells. One is tempted to suggest that, as a result of the alimentary disturbances which are present, poisons are absorbed which affect mainly the *heart* and *nervous system*. In the *wet* form of the disease, the circulation is chiefly affected : dilatation of the heart, rapid feeble pulse, dropsy which may be extreme and general, are the main symptoms. In the *dry* form the nervous system is extensively involved : there is tenderness of the skin and deep structures, diminution and loss of the deep reflexes, wasting and paralysis of the muscles, including those of respiration. The clinical picture is very like that of multiple neuritis, especially the alcoholic form of that disease.

Birds (pigeons) develop beri-beri on a diet of polished rice. The onset of nervous symptoms (in pigeons) takes place after 15 to 25 days : the head is retracted, weakness is marked, and convulsive seizures occur in which the animal turns " cart-wheels " backwards at intervals. If the diet is made more satisfactory in other respects (*e.g.* by the addition of butter fat and raw onions) the general health is better maintained, symptoms set in later, and paralysis is not present. McCarrison has described striking *alimentary* changes in these birds—congestion, interference with secretion of the digestive juices, diminished movements, and bacterial infection ; degenerative changes are also noted in the *heart*, liver, pancreas, and kidneys.

Beri-beri may be prevented or treated by administering the vitamin and remedying the *multiple* deficiences in the diet, and especially by the substitution of whole rice and wholemeal flour for polished rice and white flour.

Jansen and Donath [1] claim to have isolated the " anti-beri-beri " factor in a pure crystalline form. Rice polishings are first extracted with acidulated water ; the vitamin is then taken up by means of Fuller's earth, which has a selective absorptive power. The details of the purification process are very complex. Finally a crystalline hydrochloride is obtained with the probable empirical formula $C_6H_{10}ON_2.HCl$. It probably contains an iminazol ring, and the suggested structural formula is $(C_3H_7O)—C\begin{matrix}NH—CH\\ \|\\ N\ \ —CH\end{matrix}$ 0·025 mgrm. of this substance added daily to the diet of pigeons prevents the development of beri-beri. Eykman [2] has confirmed these results, and has been able to cure birds in which polyneuritis had been produced.

Pellagra-Preventing (P-P) Factor (Goldberger).[3]—Pellagra is a disease which is endemic in the Southern states of the U.S.A., Italy, Roumania, and other countries. It is characterized by (i) *gastro-intestinal* symptoms—pain, diarrhœa, passage of blood and mucus from the bowel, a raw beefy tongue due to shedding of the surface epithelium ; (ii) distinctive *skin* eruption—redness, swelling, development of blisters, and, later, shedding of the epithelium with subsequent pigmentation and atrophic changes ; the rash is most marked on the parts of the body which are exposed to the sun's rays ; (iii) *nervous* symptoms—mental deterioration (which may be extreme), atrophic paralysis, and sensory disturbances. The view that the disease is the result of an infection seems negatived by observations such as the following : the German army of occupation in Roumania during the War—where pellagra was prevalent—remained free from pellagra, though not exempt from infectious diseases such as malaria and dysentery. The following facts indicate that pellagra is a " deficiency disease " : (1) the diet used in pellagrous households differs in many respects from the normal ; (2) such diets given to eleven volunteers in a Mississippi prison resulted in six contracting the disease, but no cases developed among the other inmates ; (3) the same diet administered to dogs produces in three to four months a pellagra-like condition which is apparently identical with a spontaneously occurring canine disorder known as " black tongue " ; (4) human pellagra can be controlled—both prevented

[1] *Proc. Konink. Akad. van Wetenschap*, Amsterdam, vol. xxix. p. 1396.
[2] *Ibid.*, vol. xxx. p. 376.
[3] Goldberger, *Etiology of Pellagra*. De Lamar Lectures (1925–6), Baltimore, 1927 (full bibliography).

and cured—by modifications of the diet, *e.g.* by a generous allowance of lean meat and milk or yeast extract ; so long as the diet is adhered to strictly, remissions (which otherwise are of frequent occurrence) do not take place. The dietetic measures mentioned are equally beneficial in cases of canine " black tongue " ; (5) it has been suggested, on the basis of the results mentioned, that pellagra is due to protein insufficiency, but large amounts of casein—a protein of high biological value—though retarding the onset of symptoms, do not prevent recurrences ; the administration of 15 grms. of dried *yeast* daily (=7 grms. protein) is a very potent remedy and is equivalent in curative value to 200 grms. lean meat (=45 grms. protein). It will be noted that the P-P factor is similar in distribution to the " anti-beri-beri " factor—being present largely in yeast and also in meat and milk ; that the distribution of the two factors is not identical is suggested by the rarity with which pellagra and beri-beri are associated in the same patient. Further, when yeast is subjected to the action of high temperature in the steam autoclave for 2½ hours the P-P factor is preserved (as shown by tests on canine " black tongue "), but the anti-neuritic factor is destroyed, as shown by tests on rats : loss of weight takes place, polyneuritis may occur, and death finally results. Recently a pellagra-like condition has been induced in rats—characterized by loss of fur and dermatitis of the ears, paws, and neck—on a basal diet plus an alcoholic extract of yeast. It seems, therefore, that the anti-neuritic factor alone is extracted from yeast by alcohol and destroyed by high temperatures.

Vitamin C (Water-Soluble C, Anti-Scorbutic Vitamin).—Sources.—It is found in *fresh* food-stuffs : fruit juices, *e.g.* orange, lemon ; vegetables, *e.g.* raw cabbage leaves, raw juice of swedes, and to some extent in potatoes. It is present in small amounts in fresh milk and in raw meat juice ; pasteurized milk is nearly devoid of the vitamin. The content of fresh milk in vitamin C varies with the diet of the cow, being large in amount in summer, when the animal is fed on greenstuffs, and much less in winter. It is absent from dried seeds, but it is formed during the process of *germination*.

Properties.—It is rapidly destroyed by heating at 100° C. in the presence of *oxygen*, especially in an alkaline medium, and by drying. It is therefore absent as a rule from dried, canned, or preserved foods. It is possible, however, to preserve fruit without entailing loss of the vitamin, if the process is carried out *anaerobically*. Apples, for example, contain, when fresh, 5 per cent. by volume of oxygen. The fruit is peeled and quartered and covered with weak salt solution to prevent access of air ; all the contained oxygen is used up in thirteen hours by the still living and respiring fruit. Canning and cooking can then be carried out anaerobically and the fruit stored for as long as nine months and still remain rich in vitamin C.

Effect of Absence from Diet.—The absence of vitamin C from the diet produces a condition called *scurvy*. Guinea-pigs readily develop this disease when fed on a diet of oats, bran, and milk heated at 100° C. to destroy the vitamin. Growth continues for some three weeks ; weight is then lost, and death results from intercurrent infection about three weeks later.

Scurvy occurs in *infants* who have been fed exclusively on sterilized artificial food, the vitamin content of which has been destroyed. The characteristic symptom is *hæmorrhage* from various parts. After being fed for about six months on the defective diet, fretfulness and loss of appetite develop. Hæmorrhages occur—(i) under the periosteum at the lower end of

the femur, giving rise to great pain, tenderness, and refusal to use the limb ; (ii) from the gums if the teeth have erupted ; (iii) from the kidney, intestine, and under the skin. The long latent period is noteworthy.

In *adults*, scurvy occurs in sailors, prisoners, etc., deprived for a long time of fresh food ; but with a better insight into the causation of scurvy, it has been practically stamped out.

If not treated, scurvy may prove fatal from the occurrence of diarrhœa or pneumonia. It is readily cured or prevented by adding small quantities of food rich in vitamin C (*e.g.* orange juice).

The mode of action of vitamin C is unknown. The coagulability of the blood is normal. The hæmorrhages may be due to changes in the vessel walls. It has been suggested that this vitamin controls the nutrition of the endothelium of the capillaries.

Vitamin D (Anti-Rachitic Vitamin).—The distribution of the anti-rachitic factor in nature is very similar to that of vitamin A. That the two substances are distinct, however, can be easily shown : (1) vegetable oils contain some vitamin D but no vitamin A ; (2) butter fat is rich in vitamin A, but is a poor anti-rachitic agent ; (3) cod-liver oil loses its vitamin A content by combined heating and oxidation, but remains, nevertheless, a potent anti-rachitic substance ; (4) vitamin A gives an ultramarine colour with arsenic chloride which is not given by vitamin D ; (5) vitamin A is destroyed by sunlight, but vitamin D is *synthesized from ergosterol* under the influence of sunlight and other radiations (cf. p. 449).

Rickets is a disease which is due to lack of vitamin D in the diet : it is characterized by bones which are deficient in calcium phosphate, and is accompanied by a diminished calcium and inorganic phosphate content of the blood. The normal inorganic phosphorus of the serum is 5 mgrms. per 100 c.cm. ; in rickets it may fall as low as 1·5 mgrms. Rickets is a common condition developing about the sixth month of life and lasting sometimes for several years with remissions and final healing. The bones are soft and become easily bent under the weight of the body. Normally, the epiphyseal line is a well-defined narrow strip of cartilage 2 mm. deep, behind which regular ossification is occurring. In rickets the epiphyseal line is a wide irregular band. The cartilage composing it proliferates excessively, but becomes converted in a very irregular and patchy manner into tissue which resembles bone, but is very deficient in lime salts. During the active stage of the disease, the loss of calcium and phosphate in the excreta is large and may exceed the intake, suggesting that calcium may be actually removed from bone previously calcified. Healing is associated with excessive retention of calcium and phosphate. Three ætiological factors must be discussed in their relation to rickets : (1) vitamin D ; (2) calcium and phosphorus content of the food ; (3) radiant energy.

(1.) Mellanby found in prolonged dietetic experiments on puppies that when a diet of separated milk, bread, meat, and a fat like olive oil or linseed oil was administered, rickets developed if enough food was eaten to allow of fair growth. If the fat was replaced by a more potent one, the disease was prevented or cured. The order of potency of the fats was found to be—(i) cod-liver oil ; (ii) animal fats (beef-suet, lard) ; (iii) vegetable fats (peanut and coco-nut oil best, olive and linseed oil worst). The yolk of eggs, too, was potent. He concluded that these food-stuffs contained a

substance (now called vitamin D) which prevents the development of rickets.

Excessive consumption of *cereals, i.e.* bread, produces a larger increase in weight and a more severe form of rickets if the diet is deficient in the vitamin. The effect is apparently not solely due to the carbohydrate of the flour. It is not understood why cereals antagonize the action of vitamin D.

It is very difficult to induce rickets in puppies over three months of age. Similarly, rickets in children tends to heal spontaneously after the age of two years even if the diet and the environment are unaltered.

(2.) **Calcium and Phosphorus Content of Diet.**—It is obvious since calcium phosphate is the chief mineral constituent of bone that the proper deposition of this salt must depend on an adequate calcium and phosphorus content of the food. Diets which are poor in calcium or phosphorus alone usually result in the formation of bones which are excessively light, or in the development of a state of mild rickets. A diet which contains Ca and P in *unbalanced* amounts (and is also deficient in vitamin D) can produce rickets in rats with great regularity, *e.g.* a diet consisting of patent flour, 95 grms. ; calcium lactate, 2·9 grms. ; ferric citrate, 2·0 grms. ; sodium chloride, 0·1 grm. The ratio of calcium to phosphorus in this diet is 4 : 1. The excess calcium unites with most of the phosphorus and is excreted with it in the fæces. The animal, though given enough phosphorus in the diet, absorbs very little, and so rickets results. Similarly, excess phosphorus in the diet produces rickets from calcium deprivation. Such animals are employed to determine the distribution of vitamin D in foods.

Making an otherwise inadequate diet *acid* in reaction may prevent it producing rickets. The presence of the acid does not allow the formation of the more insoluble basic calcium phosphate in the bowel. Enough Ca and P are consequently absorbed into the blood to prevent rickets.

An adequacy of vitamin D appears to be able to overcome any disturbance produced by lack of balance of the mineral constituents of the diet.

(3.) **Radiant Energy.**—Palm, in 1890, drew attention to the relationship between lack of exposure to sunlight and the incidence of rickets. It is well known, too, that rickets tends to appear after the dark winter months, and to be healed during the bright summer months.

It has been shown that rickets can be prevented or cured by exposure to various forms of radiant energy, *e.g.* the quartz mercury vapour lamp, carbon arc lamp, and sunlight. The ultra-violet rays are the active ones, chiefly those having a wave-length of 300 $\mu\mu$ or less. If sunlight is filtered through ordinary plate glass, which absorbs the ultra-violet rays, it loses its potency. The minimum dose of radiation for white rats does not protect black rats. This may perhaps be due to the greater absorption of the rays by their skin pigment. This observation may explain the greater susceptibility of negro children to rickets in northern climates. The radiation may be applied to any part of the body, and yet can cure the rickety bones generally. As previously mentioned, irradiation of ergosterol (a complex fat found in traces in impure cholesterol) converts it into a highly potent anti-rachitic substance, $\frac{1}{10000}$ mgrm. daily of which will protect young rats against this disease. It is believed that ultra-violet rays similarly convert the ergosterol in the skin into vitamin D, and thus effect the cure of rickets.

Mode of Action of Vitamin D.—Robison has shown that growing bone contains an enzyme capable of splitting hexose phosphate, which is a normal constituent of blood, especially of the red corpuscles, into inorganic phosphate; excess calcium phosphate is thus formed and is precipitated. This enzyme, however, is present in normal amounts in rachitic bone. It is likely that rickety animals are capable of forming bone normally were there enough calcium and phosphorus in the blood which is supplied to them.

If the cartilage and bone of rachitic rats are placed in the serum of rachitic rats and incubated for several hours, no calcification occurs. If the same cartilage is placed in *normal* serum, calcification takes place similar to that found in an animal undergoing cure (Shipley). Similarly calcification occurs in aqueous solutions containing adequate amount of calcium and phosphate, but not if the concentration of these salts is too low.

The primary disturbance in rickets is probably *failure of absorption of calcium and phosphorus from the intestinal tract*, which results in a lowering of the calcium and phosphate concentrations of the serum. Under experimental conditions a contributory factor may be an unbalanced mineral content of the food as already explained. The anti-rachitic vitamin, or ultra-violet rays which synthesize the vitamin, is necessary to enable adequate absorption of calcium and phosphorus to take place even from a diet with a well-balanced mineral content. If a normal level of blood calcium and phosphorus can be restored and maintained, ossification proceeds normally, and the rickets is healed. It is interesting to note that Hess has shown that there is a seasonal variation in the inorganic phosphate of the blood in children. It falls during the winter, reaching its minimum in March, and rises again to its maximum in the late summer. Greater absorption of phosphate probably takes place in the summer owing to synthesis of vitamin D in the skin by ultra-violet rays.

Bacterial infection, lack of exercise, or warm, stuffy, moist atmosphere are not factors of importance in the production of rickets.

It is well known that cases of rickets are particularly liable to intercurrent infection, especially of the respiratory and digestive tract. The softened state of the ribs and the deformities of the chest may predispose to the pulmonary affections. Diets deficient in the anti-rachitic substance are probably inadequate in vitamin A content too. We have already noted that this latter vitamin aids the local defence mechanisms of the mucous membranes of the body. *Tetany* may occur as a complication of rickets owing to the lowered serum calcium (cf. p. 162).

Osteomalacia.—This is an uncommon disease, rarely met with in this country. It is fairly common in some parts of China, where it affects 1 to 3 per cent. of child-bearing women. The disease is limited to the female sex, and the symptoms usually appear during pregnancy or the puerperium. Sometimes it first manifests itself at puberty. The bones—especially the pelvic girdle, ribs, and femora—become soft and deformed. Deformation of the pelvis may be so severe as to necessitate Cæsarean section to procure delivery of the child. Symptoms usually recur with each succeeding pregnancy, but tend to clear up after lactation is completed.

During the active stage of the disease, calcium loss is occurring—*i.e.* the calcium excreted exceeds the amount ingested, and this drainage of calcium from the bones is presumably the cause of their softening. The diet of these

women is very inadequate ; it contains an excess of cereals, very little fat, and the calcium content of the food is minimal. The serum calcium is low, *e.g.* 5·8 to 7·5 mgrms. per cent. ; the inorganic phosphorus of the blood is variable – it is low or normal. Administration of calcium salts alone does not relieve the condition. The administration of cod-liver oil cures or prevents the disease and restores the normal serum calcium level.

Osteomalacia thus appears to be a form of adult rickets which is due to inadequate absorption of calcium owing to a deficiency of vitamin D and calcium in the diet ; the onset of symptoms during pregnancy and lactation is presumably due to the demands made by the fœtus and the mammary gland on the calcium reserves of the mother. There is no evidence of disease of the ovaries or of the parathyroid glands. Owing to the low level of serum calcium, *tetany*, which may be very severe, is a common complication. It is interesting to note that the bones of the *fœtus* show no signs of rickets, but merely rarefaction (*osteoporosis*). Ovariotomy may cure the condition, possibly by terminating the pregnancy.

It is convenient to summarize here the main facts of calcium and phosphorus metabolism.

Calcium Metabolism.—*Sources.*—Calcium is chiefly derived from milk, green vegetables, animal tissues, and blood.

Absorption.—Occurs in the form of soluble calcium phosphate (p. 449).

Excretion occurs mainly in the fæces and to a slight extent in the urine (p. 391). The level of the serum calcium (normal 8 to 10 mgrms. per 100 c.cm.) depends on : (i) Parathyroid hormone (p. 159) ; (ii) anti-rachitic substance (p. 448) ; (iii) blood reaction (p. 161) ; (iv) calcium phosphorus ratio in the diet (p. 449).

Rôle in the Body.—(i) Ossification of *bone* (p. 448) ; (ii) Excitability of *nerve* and prevention of tetany (p. 158) ; (iii) contraction of *heart* muscle (p. 242) ; (iv) Activation of *trypsinogen* (p. 390) ; (v) clotting of *milk* (p. 433) ; (vi) clotting of *blood* (p. 184) ; (vii) *permeability* of capillary endothelium (p. 306).

Phosphorus Metabolism.—*Sources* : It is found in milk and dissolved in all cells as inorganic phosphate. It is present in organic combination in nucleo-proteins (p. 433), phospho-proteins (*e.g.* caseinogen of milk, ovalbumin of eggs), phospho-lipines, *e.g.* lecithine, which is present in nervous tissues (brain), egg-yolk, liver, and pancreas, and as phosphagen in muscle (p. 355).

Absorption presumably occurs as inorganic phosphate. The level of the inorganic blood phosphate (5 mgrms. per 100 c.cm.) depends on the anti-rachitic vitamin, ultra-violet rays, and the calcium phosphorus ratio in the diet. Organically combined phosphorus is present in blood in the form of lecithine-like bodies.

Excretion takes place in combination with basic radicles in the urine and fæces (cf. pp. 465, 466).

Rôle in the Body.—(i) Ossification of bone (p. 448) ; (ii) regulation of blood reaction (p. 223) ; (iii) regulation of reaction of urine (p. 470) ; (iv) liberation of H_3PO_4 of nucleo-proteins (p. 433) ; (v) carbohydrate metabolism : rôle in muscular contraction (p. 355), and influence of insulin (p. 425) ; (vi) fat metabolism : formation of lecithine (p. 430).

Vitamin E is essential for normal fertility in rats. It is a fat soluble body which can be extracted with alcohol, ether, benzene ; it is stable to heat,

light, oxidation, and strong acids or alkalis. It is found in highest concentration in the embryo of *wheat*, in most commercial oils (*e.g.* olive oil), in seeds and green leaves ; there is little in milk fat and none in cod-liver oil. It is present, but not in high concentrations, in animal tissues, chiefly in the fat and muscles.

Effects of Absence of Vitamin E.—In the *male* atrophy of the seminiferous tubules eventually occurs. In the *female* rat, œstrus, ovulation, coitus, and implantation of the ovum in the uterus occur normally. The embryo develops normally until the eighth day ; further growth proceeds slowly and before the twentieth day death of the fœtus occurs. The maternal part of the placenta may go on growing and the mother increases in weight, suggesting that the vitamin is essential only for fœtal development. The embryo shows maldevelopment of blood vessels, blood cells, yolk sac, and allantois. If the vitamin is given on the fifth day of pregnancy the fœtus can still be saved. If animals are fed on diets rich in E and then placed on diets from which the vitamin is absent, they retain fertility for three or four months. Excess of vitamin E cannot increase fertility beyond the normal (Evans).

It is important to note that when the diet is deficient in vitamin *A*, sexual maturity occurs later and ovulation is infrequent ; there is extensive keratinization of the vagina and continuous shedding of horny cells which obscures the normal changes which occur during the œstrus cycle (cf. p. 444).

Rôle of Pigments of Food.—A peculiar deficiency disease has recently been described in the dog (Underhill and Mendel).[1] The condition is produced after a latent period of several months by a diet consisting of dried peas, cracker-meal and cotton-seed oil. The symptoms are (i) refusal to eat ; (ii) red line of inflammation on the gums ; (iii) development of pustules on the inner side of mouth, cheek, and lips, and on the skin ; the back of the tongue is covered with a thick yellow membranous exudate ; there is a foul stench from the mouth and intense salivation ; (iv) intense congestion of the intestines and bloody diarrhœa ; death often results in convulsions. The diet is low in inorganic salts, in vitamin A content, and in nitrogen ; but rectifying these defects does not prevent the disorder, though a high protein diet (meat) may considerably delay the onset. The disease may be prevented by the administration of pigs' liver fat or butter fat, and the latter may also cure the condition ; the potency of butter fat runs parallel to its yellow *colour*. Boiled unpeeled carrots are more effective than butter fat and the active substance can be extracted with liquefied lard and appears to be the pigment *carotin* (or something adsorbed on to it) ; crystallized carotin is highly potent both for prevention and cure. These observations suggest that the naturally occurring pigments which are present in food may play an important rôle in nutritional processes.

Nutritional Œdema.—During times of war and famine, when the amount of food available is insufficient, œdema of a " renal " type (but with no albuminuria) develops in many members of the community. There is emaciation, weakness, anæmia, and gastro-intestinal disturbances. In Poland during the war many people had no meat for months, and the staple article of diet was potatoes, supplemented by small amounts of soup and bad bread on certain days. If 5 lb. potatoes are eaten daily, diarrhœa results,

[1] Underhill and Mendel, *Am. Journ. Physiol.*, 1928, vol. lxxxiii. p. 589.

and most of the food is passed in the fæces. The *caloric* value of the diet was low, *e.g.* 1200 to 1400 calories daily, the *protein* content was low, *e.g.* 30 to 50 grms., the *fat* content was deficient, and large amounts of *fluid* and *salt* were ingested. Under such conditions œdema of a severe type develops which is not related to vitamin deficiency, but to the abnormal characters of the diet mentioned. An adequate diet cures the condition. If convalescent patients are put back on a diet of carrots and water the œdema returns. External cold and muscular work make the condition worse by increasing the caloric requirements of the body. Œdema, which may be similarly produced, develops in the course of marasmus and gastro-intestinal disorders of infancy (Maver).[1]

Essentials of a Diet.—An adequate diet must have a *caloric* value sufficient to provide for the requirements of the basal metabolism, the stimulating action of the food-stuffs, loss of energy in the excreta, and the needs of muscular work. It must have adequate amounts of *protein*, *fat*, *carbohydrate* and *salts* in suitable proportions, and an ample *vitamin* content.

Energy Requirements.—A distinction must be drawn between the energy value of the purchased food and of the food after digestion. A small percentage escapes digestion and absorption and is eliminated in the fæces, the loss being greater on a vegetable than on an animal diet. It is usual to deduct 10 per cent. from the theoretical calorie value of the mixed diet to allow for this loss. Thus a ration with a theoretical calorie yield of 1100 would only provide 1000 calories in the body.

The *basal* energy requirements can be calculated from the surface area, *i.e.* 40 C. per sq. metre per hour in the male and 37 C. in the female (p. 318). An increase of about 20 per cent. in the metabolism is produced by moving about a room, carrying out the small activities of daily life, and being exposed to fluctuations in external temperature ; the ingestion of food stimulates the metabolism to the extent of 10 per cent. It is further assumed that the *average* amount of work done daily can be represented by eight hours continuous moderate work. A young man may perform in eight hours without fatigue about 100,000 kilogram-metres of work in raising his body by going up a staircase ; this is equivalent to 240 C. when expressed in heat units. If the mechanical efficiency is 25 per cent. the total energy liberated during the process in $240 \times 4 = 960$ C. The day may be divided into three periods of eight hours each—of sleep, rest, and work. In an average working *man*, with a surface area of 1·8 sq. metres the total energy requirements are as follows :

8 hours sleep (basal) $= (40 \times 1{\cdot}8) \times 8$	= 576 C.
8 hours awake = basal + 30 per cent. (+10 per cent. for dynamic action of food + 20 per cent. for "minor activities")	= 749 C.
8 hours work = basal + 960 C.	= 1536 C.
Add for travelling between home and place of occupation and general locomotion	= 300 C.
	3161 C.

It is interesting to note that in Great Britain determinations of the total energy expended by different classes of workers have given an average figure

[1] Maver, *Journ. Amer. Med. Assoc.*, 1920, p. 934.

of about 3000 C. per diem. The energy requirements of *working women* are about 2400 C.; this includes an allowance of 200 C. for the carrying out of household duties. The various occupations may be classified as follows as far as the energy requirements of the *work* are concerned: (i) sedentary, less than 400 C.; light work 400–700 C.; moderate work, 700–1100 C.; heavy work, 1100–2000 C. All classes of brain work must be classed among the sedentary pursuits; even the most intense mental activity causes no appreciable increase in the metabolism. The energy requirements of a purely sedentary home worker do not exceed 2100 C.

Children.—The energy needs of children are very difficult to compute. The basal metabolism is considerably greater per sq. metre of surface in children than in adults (p. 319). Greenwood has calculated from the scanty data available the 24-hour *basal* requirements in calories of boys and girls.

Age.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.
Boys . .	1026	1100	1159	1197	1262	1328	1358	1389	1430	1499
Girls . .	1008	1057	1110	1163	1201	1266	1321	1399	1476	1539

The fact that *growth* is occurring implies that excess of energy must be taken over and above that required to furnish the energy output of the body. Between the ages of 11 and 16, both sexes put on weight at the average rate of about 4 kgrms. a year. This is equivalent to only 30 C. per day; but the growing body is formed at the expense of many different varieties of food which have to undergo chemical conversions of different kinds before they can take their place as part of the living body, so that probably the amount of energy which must be provided in the food to produce the necessary increase in weight is considerably in excess of 30 C.

It is still more difficult to compute the energy output due to muscular *activity* in children. Probably any reduction of the ration will cause a diminution in activity, before it effects the processes of the body which are essential to health and growth. This may explain the remarkable discrepancy between the diet allowed to the over-exercised children of the wealthier classes and that on which the children of the working classes obtain satisfactory development. Lusk gives the following table to show the total food requirements of children in relation to that of an average man or woman:

Age.	Coefficients.	Utilizable Calories.
Average man . . .	1·0	3000
Average woman . . .	0·83	2500
0–6 (both sexes) . .	0·5	1500
6–10 (,, ,,) . .	0·7	1800
10–14 (,, ,,) . .	0·83	2500
14–20 (boys)	1·0	3000
14–20 (girls)	0·83	2500

Under-Nutrition.—Benedict placed twelve subjects with a food consumption equivalent to 3100 C. per day on to a diet containing only 1600–1800 C. They all became thinner and after 5 weeks had lost 10 per cent. of their body weight. They were then given 1967 C. daily and the body weight remained stationary for several months. At first it appeared that the economy in food was accomplished without untoward effects, but as the experiment proceeded it became obvious that the men were incapable of their normal degree of physical exertion, they lacked vitality and tired easily, and there was very definite lessening of sexual desire ; the mental powers were not appreciably affected. A similar experiment on a huge scale was carried out in the Central European countries owing to the exigencies of the Great War. The dietary was reduced to 2500 C. except for workers in factories and fields ; after apparently favourable results at the commencement, marked deterioration in the health and endurance of the population soon became evident.

Starvation (see p. 441).

Before dealing with the proportion of protein, fat, and carbohydrate that should be employed, the composition of the common food-stuffs must be surveyed (see Table, p. 456).

The percentage *carbohydrate* content of the different classes of food are : cereals, 66 to 75 ; meat and poultry, eggs, fish, butter, olive oil, nothing or a trace ; milk 5 ; cheese 24 ; peas and beans 60 ; potatoes 14 to 18 ; fruits 4 to 14 ; starch 90 ; sugar 100.

The percentage composition of *bread* is : protein 9·0, fat 1·5, carbohydrate 53, calories 1200 per 1 lb.

The constitution of a normal diet has been given somewhat differently by different authorities.

	Average Man.[1]	Soldier Manœuvres.[2]	Soldier (War-time).[3]
Protein . .	100 grms.	135 grms.	145 grms.
Fat . . .	100 ,,	80 ,,	100 ,,
Carbohydrates .	500 ,,	500 ,,	500 ,,
Calories . .	3390 ,,	3348 ,,	3575 ,,

[1] Royal Society Food (War) Committee. [2] and [3] from Voit.

Protein.—Protein is an essential constituent of the diet because it is the only class of foodstuff containing nitrogen (and sulphur) in a form which can be assimilated by the tissue cells and used for the replacement of that lost as a result of the normal activities of the cells.

Anywhere in the world except among the destitute, the protein consumption does not fall below 1 grm. per kilogram per diem, or 70 grms. for a man of average weight ; in N. Europe and the U.S.A. the figure is more like 1·3 grm. to 1·5 grm. per kilogram or about 100 grms. per man. The amount of protein consumed varies directly with the wealth and social position of the individual ; it is not increased in the case of men doing hard work. Thus the lumbermen of Maine or Sweden, who consume 8000 to 9000 calories daily, obtain only 10·5 per cent. of their calories from protein and about 58 per cent. from fat.

TABLE OF COMPOSITION AND CALORIE VALUE OF MORE IMPORTANT FOOD-STUFFS ADOPTED BY THE INTER-ALLIED SCIENTIFIC FOOD COMMISSION.

(The carbohydrate content is not quoted, but is taken into account in calculating the energy values.)

Calorie values per 1 grm.: protein=4·1; carbohydrate=4·1; fat=9·3.

Commodity.	Protein. Per cent.	Fat. Per cent.	Calories. Per kgrm.
Cereals.			
Wheat and Barley flour	11·5	1·0	3640
Oatmeal	16·0	8·0	4000
Barley meal	10·5	2·2	3600
Rice	8·0	0·3	3540
Meat.			
Beef (Pre-War)	14·5	22·5	2690
,, (War)	15·0	18·0	2290
Veal	16·0	6·3	1230
Mutton	13·5	24–30	2790–3340
Bacon	9·5	60·0	6000
Ham	14·5	34·0	3750
Poultry and Game	15·0	9·5	1500
Herrings	11·6	4·0	850
Fresh Fish	10·0	1·0	500
Dairy Produce.			
Eggs at 2 oz.	12·0	9·5	1400
Milk	3·3	3·7	700
Butter	1·0	85·0	7950
Cheese	25·0	30·0	4000
Margarine	1·2	83·5	7800
Lard	2·2	94·0	8800
Fresh Fruit.	av. 0·7	0·4	500
Nuts	6·5	22·8	2600
Potatoes	1·8	0·1	700
Shelled Peas and Beans	7·0	0·5	1000
Dried Peas	24·3	1·3	3600
Refined Sugar	..	..	4100
Cocoa	15·0	34·0	4800
Olive oil	..	100	9300

The minimum amount of protein needed for tissue repair is probably 30 to 40 grms. per day, provided that the protein is of the proper constitution. On such a ration, if enough carbohydrate and fat are consumed to provide the full energy requirements of the individual, nitrogenous balance may be maintained. But (as pointed out on p. 442) with certain kinds of protein it is impossible to obtain nitrogen balance no matter how much is ingested. Proteins which are deficient in any of the essential amino-acids are of inferior biological value and cannot in themselves produce healthy development.

Experiments have been carried out by Chittenden, Hindhede, and others in which nitrogenous equilibrium and unimpaired health and mental and physical vigour have been maintained for months or years on diets which contained no more than 30 to 50 grms. protein daily. But the proteins were specially selected and were of high biological value. To provide a margin of safety when consuming a mixed diet, a minimum of 80 grms. should be arrived at, and this tallies better with the general experience of mankind. Bayliss said, "Take care of the calories and the proteins will take care of themselves," because if dietaries are studied it is found that if the calorie value of a mixed diet is adequate it will probably contain 100 grms. of protein or even more.

Animal proteins are usually regarded as far superior to vegetable proteins, but the proteins of potato are among the most valuable. *Isolated* plant proteins such as gliadin or zein are very inadequate, but the mixed proteins of wheat or maize as found in flour or meal will maintain nitrogenous equilibrium at a fairly low level, particularly if whole grain is used and if it be supplemented by small quantities of other proteins such as those of milk. In any mixed diet, even if wholly of plant origin, the proteins are sure to be sufficiently varied to compensate for any individual inadequacies, if only the total amount of protein is sufficient (Greenwald).

Fat.—The amount of fat consumed varies with the country, economic status, occupation, and the time. The maximum fat content of the really native diets in Japan is about 30 grms., which is (except during the War period) the European minimum. The amount of fat eaten increases steadily with the income ; the Inter-Allied Food Commission adopted 57 grms. daily as the minimum fat ration during the War. Experiments of short duration have been carried out in which health and weight were maintained on diets of high total calorie value with as little as 10, 13·8, and 13·9 grms. of fat daily. Although the body can adapt itself to partial or even complete deprivation of fat for short periods (probably preparing the necessary fat from the carbohydrate of the food), deleterious effects will become apparent after months or years. The significance of fat in the diet depends on several factors. It is highly assimilable and is almost entirely absorbed from the alimentary canal. But its absorption is a gradual process, not reaching its maximum till five or six hours after a meal. Man is unaccustomed to work with the alimentary canal entirely at rest, and when the digestion of the last meal is finished, hunger recurs and affects the efficiency of the work. The bulk of the food becomes of importance when the total energy requirements of the body are very large. Weight for weight, fat has double the calorie value of starch or sugar. Fat, in addition, is taken without admixture in a pure form, whereas the other foods are all mixed with a considerable proportion of water ;

when starch is cooked it is swollen up with five to ten times its volume of water. As has been pointed out, the Swedish and American lumbermen and the Welsh miners obtain a large part of their huge calorie intake from fat. Carbohydrates are more subject to fermentative changes in the intestine, with the production of gases and general discomfort. A study of dietaries shows that a normal diet of 3000 C. should contain 75 grms. fat (698 C.) ; the fat ration should always be high if there is a large increase in the energy expenditure of the body, either in the form of work or in consequence of exposure to cold (Starling).

The animal fats are the most important sources of some of the vitamins, *i.e.* A and D (pp. 443, 448). The vegetable fats are an equally effective source of energy, but are deficient in vitamins, except E (p. 452). It is advisable from the point of view of the health of the community that margarine should not be made exclusively from vegetable oils, but should have added to it animal fats (not lard) or milk fats.

Carbohydrates furnish more than 50 per cent. of the energy content of most diets, and are a cheap and readily obtained food. If the amount of carbohydrate ingested is greatly reduced in amount, the fats are incompletely oxidized and give rise to poisonous bodies such as β hydroxy-butyric acid and aceto-acetic acid. As both carbohydrate and fat serve chiefly as sources of energy, they can replace one another to a considerable extent, so long as precautions are taken to ensure the minimum amounts of fat specified above.

The *mineral* constituents of the human body amount to 4·3 to 4·4 per cent. The only salt commonly consumed as such is sodium chloride. The various salts needed by the body are present in small amounts in the food, particularly in milk and in vegetables. 1 to 2 grms. of NaCl are needed daily, and while custom varies considerably the average intake is probably nearly 8 to 10 grms. Possibly habit has resulted in the use of much more NaCl in the human dietary than is physiologically necessary. 0·9 to 1 grm. of *calcium* is needed daily (Sherman), and the minimum necessary for the maintenance of a calcium balance is 0·63 grm. calcium per 70 kgrms. of body weight. Fifteen per cent. of the American diets investigated by Sherman were found to be deficient in calcium. A sufficient calcium supply is very important, especially in children, and is best obtained by the ingestion of liberal quantities of milk. 0·88 grm. of *phosphate* is the minimum needed per 70 kgrms. body weight, but there is no risk of phosphorus shortage in diet yielding 3000 C. daily unless large amounts of degerminated patent flour are consumed as the principal cereal. The daily intake of *iron* should be not less than 12 mgrms. daily, a figure which should be increased in pregnancy and in lactation. It is now advised that infants shall be given small amounts of soups prepared from marrow bones and mixed vegetables from the third month onwards, partly to prevent the anæmia which develops on a purely milk diet (cf. p. 214). *Iodine* in minute traces is essential for the preparation of thyroxine, the active principal of the thyroid gland. In districts in which the iodine supplies in the drinking water are insufficient, simple goitre frequently develops. This may be prevented, or the condition may be cured, by the use of iodised table salt, or by the deliberate addition of iodine to the water supply (p. 154).

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X

THE SECRETION OF URINE

Kidney—Structure—Blood supply—Nerve supply—Functions of kidney—Of glomeruli—Composition of glomerular filtrate—Importance of blood-flow—Concentration by kidney—Nature of reabsorption—Secretion—Dilution diuresis—Tubule diuresis—Water drinking—Urea concentration—Concentration of salts—Blood reaction—Rôle of pituitary—Water intoxication—Nephritis—Uræmia—Causation.

Structure of the Kidney.—The renal tubule consists of the following parts: (1) Bowman's *capsule*, into which is invaginated a tuft of capillary vessels, the *glomerulus*; the capsule and glomerulus together constitute the Malpighian [renal] corpuscle. The capsule is lined by a syncytium where it is reflected over the glomerulus, and elsewhere by a layer of flattened cells. (2) *First convoluted* and *spiral* tubules, which are lined by a cubical epithelium; the free border of the cells is striated ("brush border"); they contain columns of granules arranged vertically to the surface, and often watery vacuoles as well. (3) *Descending loop* of Henle, lined by flattened cells leaving a large lumen. (4) *Ascending loop*, lined by cubical cells leaving a small lumen. (5) *Zig-zag* and *second convoluted* tubules lined by the same epithelium as 2. (6) *Collecting* tubules, lined by clear cubical cells. (7) *Ducts* of Bellini, lined by clear columnar cells; they open at the apex of the pyramids. The loops of Henle, the collecting tubules, and the ducts of Bellini lie in the medulla of the kidney; the other parts of the tubule are found in the cortex. It is important to note that the length of the human renal tubule is about *3 cm.*; the diameter is 20 to 60 μ.

Blood Supply.—The renal artery divides into branches, which run between the pyramids to the "boundary zone" between the cortex and the medulla, where they are united by a series of *arterial arches*, with their convexity directed outwards. A series of parallel *cortical* or interlobular arteries passes outwards and gives off at intervals the afferent vessels of the glomerulus, which enter the capsule and break up into capillary tufts. A smaller efferent vessel emerges and breaks up into capillaries over the walls of the convoluted tubules. From the concavity of the arches, parallel vessels enter the medulla—the *arteriæ rectæ*—which break up into an elongated capillary meshwork over the loops of Henle and the collecting tubules. The veins accompany the arteries; the venous arches lie in the concavity of the arterial arches. The *venæ stellatæ* under the capsule connect up the renal and perirenal veins. Richards and Schmidt[1] have shown by direct

[1] *Amer. Journ. Physiol.*, 1924, vol. lxxi. p. 178.

microscopical observation of the frog's kidney (*v. infra*) that only a proportion of the glomeruli may be functioning at one time ; indeed, a flow may be seen in some, and not all, of the capillaries of any one glomerulus. By injecting various substances intravenously and subsequently examining the glomeruli histologically, it has been shown that the same arrangement holds good for the mammalian kidney. In the anæsthetized rabbit, 56 to 90 per cent. of the glomeruli are patent ; this number is markedly reduced by the injection of adrenaline, while the administration of diuretics may cause all the glomeruli to open up.

Nerve Supply.—The sympathetic connector cells lie in Th6 to 12; the excitor cells lie in the renal ganglion in the hilum of the kidney. Grey fibres supply the arterioles and have also been traced to the tubules. It is probable that the nerves have no direct influence on the activity of the kidney except by modifying its blood supply.

Functions of the Kidney.—A great deal of attention is usually paid to the manner in which the kidney elaborates the urine. The rôle which the kidney plays in the body often receives less consideration. It may be said that the kidney regulates the *osmotic relations* in the tissues and in the blood, and maintains the *optimum concentration* of the individual constituents of the plasma. It serves to eliminate *waste products*, particularly the nitrogenous bodies formed during the processes of metabolism. It gets rid of most of the *basic* and the non-volatile *acid* radicles which are formed in the body or are taken in the food. It helps to keep constant the *volume* of the circulating blood, and aids in preserving the *reaction* of the blood within narrow limits. These functions are not distinct, but are closely inter-related. It eliminates *toxic* substances which have been artificially introduced into the body ; certain substances are probably *formed* by the cells of the tubules.

Functions of the Glomeruli.—It is probable that the glomeruli allow the passage of a fluid into the lumen of the tubule which is practically *identical in composition with the plasma except for its proteins.* This fluid is believed to pass out from the blood by the purely physical process of *filtration.* The evidence can be summarized as follows :

1. Richards and Wearn [1] have been able to collect and make preliminary analyses of the glomerular filtrate formed in amphibia. A small arc lamp is arranged to throw light directly on the exposed kidney of a frog, laid on the stage of a microscope. The superficial vascular structures become visible. A fine sharp-pointed capillary pipette (10 to 20 μ in diameter) made of quartz is inserted into a suitable capsule of Bowman ; the glomerular filtrate is collected and found to have the following composition :

i. *Protein* is absent, proving that no contamination with the blood had occurred during the manipulations, and that no protein is filtered into the capsule.

ii. *Sugar.*—None could normally be detected in the blood or in the glomerular filtrate. Glucose was then injected under the skin. If the blood sugar is under 0·5 per cent., sugar is found in the filtrate, and none in the bladder. It therefore must be *absorbed* in its passage down the tubules. If the blood sugar is raised above 0·5 per cent., sugar is found both in the filtrate and in the bladder urine.

iii. *Chloride.*—The bladder urine of fasting frogs is practically free

[1] Wearn and Richards, *Amer. Journ. Physiol.*, 1924, vol. lxxi. p. 209.

from chlorides; the glomerular filtrate, however, gives a heavy precipitate with $AgNO_3$. This proves that absorption of chlorides occurs in the tubules.

iv. *Urea* and *potassium* can be detected in the filtrate. Accurate quantitative analyses of the filtrate have not yet been possible.

v. The *reaction* of the glomerular fluid has not yet been precisely determined. The fluid in the capsule is more alkaline than that lower down in the tubules.

These results show clearly that the capsular fluid closely resembles the plasma in composition. Some preliminary quantitative experiments[1] seem to show, however, that frequently the chloride concentration in Bowman's capsule may *exceed* that in the plasma.

2. Starling and Verney[2] have performed perfusion experiments on the isolated mammalian kidney with blood from a heart-lung preparation (cf. p. 262), or from a suitable pump. A flow of urine usually begins 1 to 40 minutes after the artificial circulation is started. To eliminate the activity of the tubules a weak solution of *cyanide* can be added to the perfusing fluid[3] which paralyses all oxidation processes in those cells. The fluid then obtained is regarded as capsular fluid unaltered by the cells of the tubules, and is found to be similar to plasma in glucose, sulphate, urea, and bicarbonate content.[4]

3. The glomeruli are certainly well adapted to carry out a process of filtration. The blood in the capillary tufts is only separated by two thin layers of cells from the interior of the capsule.

4. There is evidence to suggest that the pressure in the glomeruli is unusually high, *i.e.* about the same as the carotid blood pressure or 20 per cent. less (100 to 120 mm. Hg). It must be remembered that the whole of this pressure is not available for purposes of filtration. It is opposed by the plasma proteins which exert an osmotic pressure of 40 mm. Hg, which tends to hold fluid back inside the blood vessels. The "nett" filtering force is therefore $120 - 40 = 80$ mm. Hg. Filtration can therefore only proceed if the ureteric pressure is below this figure. This is found to be the case. The ureter is ligated, and a cannula is inserted above this point and connected with a mercury manometer. The pressure in the ureter, as recorded by the manometer, rises gradually to a maximum of about 80 mm. Hg and then remains stationary. In other words, when the pressure in the ureter, and consequently in the tubule and in the capsule, is 40 mm. Hg lower than the supposed glomerular pressure, the filtration of urine comes to an end. If the plasma is greatly diluted by the injection of saline and the protein osmotic pressure is reduced, filtration goes on till a higher ureteric pressure is attained, *e.g.* 100 mm. Hg.

[1] Wearn and Richards, *Journ. Biol. Chem.*, 1925, vol. lxvi. p. 247.

[2] Starling and Verney, *Proc. Roy. Soc. B.*, 1925, vol. xcvii. p. 321.

[3] Perfusion must then be carried out with the pump.

[4] In these experiments it is assumed that cyanide in no way modifies the behaviour of the glomerular epithelium, which is regarded as a purely passive membrane; but when the isolated kidney has been exposed to the action of cyanide for 10 minutes, protein appears in the urine. It is possible, therefore, that even during the first 10 minutes some modification in the permeability of the membrane has taken place; the capsular fluid collected in these experiments is not necessarily identical with that formed normally.

Similarly, it is found that if the isolated kidney is perfused with blood at a pressure of less than 40 mm. Hg, no urine is formed.

5. If the glomerulus is a mere filter, its activity should depend on the following factors: (1) Glomerular *pressure*, which is taken to move in the same direction as the general blood pressure. (2) The blood-*flow* (cf. *v. infra*) through the kidney, which may be directly determined by measuring the outflow along the renal vein, or indirectly deduced from changes in the renal volume as recorded by an oncometer. Unless special considerations have to be taken into account the kidney volume varies directly with the blood-flow. (3) Composition of the blood (p. 467). (4) Character of the epithelium. The experimental results obtained fit in with this view.

Extracts of the posterior lobe of the pituitary body ("pituitrin") (in the anæsthetized animal) raise the blood pressure (and presumably the glomerular pressure too), increase the blood-flow through the kidney, and increase the urinary output. *Adrenaline* raises the blood pressure but constricts the renal vessels, and so the flow of urine is diminished. A rise of blood pressure increases the flow of urine unless it is accompanied by vaso-constriction of the renal vessels (*e.g.* adrenaline, asphyxia). A fall of blood pressure lessens the urinary flow (*e.g.* stimulation of peripheral end of vagus, hæmorrhage, division of spinal cord in the neck), unless the kidney arteries are dilated beyond those of the rest of the body.

6. Oxygen is necessary to preserve the integrity of the glomerular epithelium as a colloidal membrane which is impermeable to protein, but which permits free passage to salts and water (see p. 462, footnote 4).

Importance of Blood-Flow.—It must be remembered that the blood-flow through the kidney probably has a more important bearing on the secretion of urine than the blood pressure.

1. The diuresis normally produced by drinking 560 c.cm. of hot tea is inhibited by muscular exercise consisting of running 1½ miles at 7 to 8 miles an hour (Pembrey). This result is attributed to the vaso-constriction of the splanchnic area and of the renal vessels which accompanies exercise; so that, in spite of the rise of blood pressure, renal activity is diminished because of the lessened blood supply to the kidney.

2. Constriction of the renal vein raises the glomerular pressure, but the blood-flow through the kidney is greatly reduced. The asphyxial condition damages the glomerular epithelium and alters its permeability so that it allows albumin and blood to escape. The fluid which is present in the glomeruli is filtered out. They then become blocked by fused masses of red blood corpuscles which finally arrest the blood-flow completely. The engorged renal veins within the kidney press upon the collecting tubules and prevent the escape of urine. It is not surprising therefore that the urinary flow is completely stopped. An analogous condition results clinically from *heart failure* with diminished arterial supply and venous congestion of the kidney.

At *night* the circulation rate is diminished and the blood pressure is lowered. Consequently the amount of urine formed is less than by day. When no excess of fluid is taken, the night urine does not exceed 450 c.cm.

Functions of the Tubules.—As the glomerular filtrate passes down the tubules, it is modified in a complex manner, as appears in the following

table (after Cushny), in which the composition of blood and of urine are compared. The extent to which the kidney concentrates the various constituents of the blood is also indicated:

Constituent.	Percentage in Blood.	Percentage in Urine.	Degree of Concentration.
Water	90–93	95	—
Proteins, Colloids, Fats	7–9	—	—
Sugar	0·10	—	—
Na	0·30	0·35	1
Cl	0·37	0·6	2
Ca	0·008–0·01	0·015	2
K	0·02	0·15	7
PO_4	0·005	0·15	30
Uric acid	0·002	0·05	25
Urea	0·02–0·04	2	70
SO_4	0·002	0·18	90
Creatinine	0·001	0·075	75

According to Cushny, the modification of the glomerular filtrate as it passes down the tubule is due *solely to a process of differential absorption*. It is obvious from the table that the various constituents of the plasma are not treated alike. *Sugar* is completely absorbed, and none appears in the urine; while other constituents (*e.g.* sulphate) are concentrated to a considerable degree. It will be noticed that creatinine and sulphate are concentrated about eighty times, and this is due, according to Cushny, entirely to absorption of water from the lumen of the tubules back into the plasma. If the tubules absorbed water only, then *all* the constituents of glomerular filtrate should be concentrated to the same extent. This is obviously not the case, however; any constituent which is concentrated less than eighty times, must itself have been absorbed, and the less it is concentrated the greater must be the extent of the absorption which takes place.

Cushny denies that any secretion (or *excretion*) of urea or other substances is effected by the tubules, *i.e.* he holds that the epithelium does *not* transfer constituents from the blood into the lumen of the tubules. Some quantitative ideas of what the kidney has to do according to this hypothesis can be obtained from studying the behaviour of urea. The normal daily urinary excretion of urea is 30 grms. As the blood urea averages 0·03 per cent., 30 grms. of urea are contained in 100 litres of plasma. On Cushny's filtration-reabsorption theory, 100 litres of plasma must filter out of the glomeruli in 24 hours; as only 1·5 litre of urine is formed daily, 98·5 litres of water must be reabsorbed; 30 grms. of urea are left behind in 1·5 litre urine (2 per cent.), which is seventy times as high a concentration as in the plasma (0·03 per cent.).[1]

[1] In this calculation the traces of urea which are possibly reabsorbed are ignored: if they are taken into account, the amount of glomerular filtrate must be greater still.

Cushny divides the constituents of the urine into two groups—*threshold* and *no-threshold* bodies.

1. *Threshold* substances are those which are of value to the economy and are reabsorbed into the circulation so as to maintain their appropriate level in the blood. Sugar, Cl, Na, and bicarbonate are examples of *high threshold* bodies, which are reabsorbed in considerable amounts, while comparatively small fractions are eliminated in the urine. The absorption of sugar and Cl has been conclusively proved for the frog's kidney (p. 461). (*a*) The threshold value for sugar is 0·18 per cent. The blood sugar is normally below this level, so all the sugar filtered through the glomeruli is reabsorbed. If the blood sugar exceeds 0·18 per cent., the excess sugar is allowed to escape in the urine. It then undergoes concentration in its passage down the tubules owing to the reabsorption of water, but rarely exceeds 10 per cent. (cf. p. 419). It is suggested that *phloridzin* acts by paralysing the power of the tubule to resorb sugar, which is therefore permitted to escape in the urine (cf. p. 418).

(*b*) Na, Cl, Ca are not usually completely reabsorbed, but only in sufficient amounts to maintain the appropriate level in the blood. According to Cushny (p. 464) about 100 litres of glomerular filtrate are formed daily, which contain 370 grms. Cl; 1·5 litre urine contains only 9 grms., so that 361 grms. Cl are resorbed. The percentage of Cl in the urine is 0·6 per cent. compared with 0·37 per cent. in the plasma, so that Cl is concentrated twofold. When a subject is placed on a salt-free diet for a week, Cl disappears from the urine completely, as it is all retained in the blood.

(*c*) K, PO_4,[1] and uric acid are reabsorbed, but to a much slighter extent, and are therefore called *medium* threshold bodies. It might be thought strange that uric acid, which is usually regarded as a waste product, should not be completely eliminated. The blood uric acid level is 0·002 per cent., so that 2 grms. are filtered daily in the 100 litres plasma which are formed in the glomeruli; only 0·75 grm. appears in the urine, so that 1·25 grms. is resorbed. It is pointed out, however, that little is known of the manner in which uric acid is carried in the blood; it may circulate to some extent in a colloid form which cannot undergo complete filtration in the glomeruli.

(*d*) Water might be included among the threshold bodies, for, as stated above (p. 464), it is claimed that very large amounts are reabsorbed daily.

2. *No-threshold* bodies are waste products or other substances of no use to the economy, which the kidney does not reabsorb under any circumstances. They are excreted so long as they are present in the blood. Creatinine and SO_4 are examples of such bodies. For all practical purposes, *urea* can be placed in this category too, though Cushny suggests that for some unknown reason small amounts are reabsorbed into the plasma; it will be noticed that urea is concentrated less than the maximal extent—only seventyfold.

According to Cushny the fluid reabsorbed by the tubules is of *unvarying* composition and resembles Ringer-Locke's solution with the addition of traces of other constituents. It is supposed to contain glucose 0·11 per cent., Na 0·32 per cent., Cl 0·4 per cent., urea 0·008 per cent., uric acid 0·003 per cent., K 0·02 per cent., PO_4 0·008 per cent. Other authorities, while accepting the absorption hypothesis, yet hold that the composition of the material returned to the blood *varies with the needs of the body*, and that it is *adjusted*

[1] Cf. p. 466.

to maintain an optimum concentration of the different constituents of the plasma.

Nature of Reabsorption.—Absorption is not a purely physical process, because the osmotic pressure of urine is considerably higher than that of blood. The tendency would be for water to pass from the blood into the tubules instead of in the reverse direction. The depression of the freezing-point (Δ) is a measure of the molecular concentration, and therefore of the osmotic pressure of a solution. The Δ of blood is $-0{\cdot}56°$ C., and that of urine is $-1{\cdot}0°$ to $-2{\cdot}5°$ or even $-5°$ C. in concentrated urine. The tubules consequently have to exert a " vital activity " and do work to return water to the blood against the osmotic resistance of the concentrated urine. The kidney, therefore, consumes much oxygen when carrying out its normal activities—about 0·4 c.cm. per grm. per minute. The urine can never be concentrated beyond the point at which its osmotic pressure just balances the absorbing power of the renal cells. Apparently there is also a limit to which the *individual* urinary constituents can be concentrated; urea, for example, rarely exceeds 4 per cent. in the urine (cf. p. 472). The solids of the urine therefore demand a certain minimum amount of water for their excretion (" volume obligatoire "—Ambard).

Time Factor.—For effective concentration to occur, the glomerular filtrate must remain in contact with the tubules for a reasonable time. The more rapidly filtration is occurring, the more the urine resembles plasma in composition, as less time is available for absorption to take place.

Starling and Verney have offered some evidence that the cells of the renal tubules, in addition to reabsorbing certain constituents, may also secrete (*excrete*) some waste products from the blood into the tubules. They compared the urine which is formed by an isolated kidney when it is perfused at constant pressure with equal volumes of normal blood and with blood containing cyanide respectively. In the first case the tubules are functioning normally, in the second their activities are paralysed owing to cessation of oxidative processes in the cells. During the period of perfusion with blood containing cyanide, there is a marked *fall in the total amount* of urea and sulphate eliminated per unit of time, and an increased rate of excretion of water and chloride. The amount of urine passed increased from 9·4 c.cm. to 19·8 c.cm. per 15 minutes—*i.e.* the normal absorption of water was not occurring. Only 95 mgrms. instead of 145 mgrms. of urea were eliminated per 15 minutes. This latter finding, they argue, proves that the tubules normally actively excrete urea and that this function is paralysed by the cyanide.[1]

There is good evidence that certain substances may be *formed* by the cells of the renal tubules and then passed out into the urine. (i) *Ammonia*: Nash and Benedict have shown that the renal vein of the dog contains two to three times the concentration of ammonia found in arterial blood, while in the blood of the lower part of the inferior vena cava the concentration is the same as in arterial blood. Bilateral nephrectomy does not raise the ammonia content of the arterial blood (cf. pp. 225, 399). (ii) *Hippuric acid*: It has been proved by perfusion experiments that the kidney synthesizes hippuric acid from benzoic acid and glycine. (iii) *Phosphate*: An enzyme (phosphatase) has been isolated from the kidney which can

[1] See, however, criticism of the technique employed (p. 462, footnote 4).

hydrolyse organic (hexose-) phosphate ; and it is suggested that the inorganic phosphate eliminated by the kidney may be in part derived from the organically combined phosphate of the plasma.

Summary.—The glomeruli *filter* out fluid which resembles deproteinized plasma ; the renal epithelium undoubtedly *absorbs* certain substances of value to the economy in accordance with the needs of the body ; it perhaps also actively *excretes* certain waste products from the blood (*e.g.* urea and sulphate), and *manufactures* substances like ammonia and hippuric acid.

Rôle of the Kidney in the Body.—The kidney acting as a whole responds to minute changes in the " internal environment of the body, and delicately regulates the composition of the plasma." If a slight excess of urea, NaCl, water, or alkali is introduced into the body, compensatory reactions occur. The stimulus to excretion or retention of substances is presumed to be the increase or diminution of their concentration in the blood, though the change in the blood may be scarcely detectable by the means at our disposal (Haldane).

1. Regulation of Fluid Content of Body and Osmotic Relationships.—Dilution Diuresis.—The intravenous injection of saline, whether hypo-, iso-, or hypertonic, causes a marked diuresis. The arterial blood pressure is little affected, and only shows a brief, transient rise (Figs. 1, 2). Direct measurement of the outflow from the renal vessels shows that the blood supply of the kidney is not increased either constantly or to any great extent. The circulatory changes in the kidney are therefore relatively unimportant. If the quantity of fluid injected is one-half to one-third the blood volume, diuresis sets in after half an hour, reaches its maximum during the second hour, and then declines. Cushny suggests that the diuresis is due to dilution of the plasma proteins, which permits of more copious filtration in the glomeruli. But when the protein concentration was reduced from 7·33 to 3·84 per cent. in one experiment, the urinary flow per minute rose from 1·2 c.cm. to 115 c.cm. Increased filtration alone cannot explain a urinary output which is a hundred times as great as normal. Cushny suggests that fluid rushes through the tubule at such a rate that the epithelial cells are overwhelmed and fail to absorb in a normal manner. Instead of only 1·5 per cent. of the volume of the filtrate escaping resorption, over 50 per cent. may pass out in the urine. The tubule may fail to absorb other important constituents of the plasma, *e.g.* Cl and sugar, which may be lost in large amounts.[1] As the excess fluid is got rid of, the blood becomes more concentrated, the plasma protein osmotic pressure returns to normal, slower filtration takes place, and more adequate reabsorption is resumed. The diuresis is therefore of brief duration.

There is *no* increased oxygen consumption during dilution diuresis, although such large amounts of urine are eliminated. The kidney is not doing more work, but has allowed the urine to pass through it rapidly without modifying it in the usual way.

Very gross changes are, however, introduced in the above experiment. The delicate regulating action of the kidney can be best studied in experiments on man.

[1] Cushny attributes the diuresis to *failure* of absorption ; but as there is an excess of water in the blood we may perhaps say that the tubules permit the water to escape rather than absorb it unnecessarily back into the blood.

Water Diuresis.[1]—If no food or drink is taken during the day after breakfast, the excretion of urine falls to about 50 c.cm. per hour and remains steadily at that level. If 2 litres of water are drunk in 15 minutes, the urinary output may rise to 1200 c.cm. per hour, or twenty-five times the normal (cf. Fig. 108 A). The specific gravity of the urine falls to less than 1001. If the hæmoglobin concentration is determined as indicating changes in the water content of the blood, it is found scarcely to alter at all, or only to fall by 2 per cent. Even when 5 litres are drunk in the course of two hours, it is found that the water can be completely eliminated in the course of the next 4 or 5 hours without any appreciable dilution of the blood having occurred. The maximum rate of excretion in normal men is about 1300 c.cm. per hour, but there is evidence that this level cannot be long maintained owing to fatigue of the kidney. A prolonged excretion of 750 c.cm. urine per hour can be kept up for many hours (Priestley).

If 2 litres of water are drunk, absorption is rapidly effected, but, as stated, little dilution of the blood occurs. The excess fluid which cannot be immediately excreted is temporarily accommodated in the *tissue spaces* in the muscles and in the skin. This fluid is later gradually mobilized from the regions where it is stored and eliminated by the kidney. In the light of the experiments quoted on p. 467, one may attribute the diuresis produced by water-drinking to the slight dilution of the plasma which increases filtration in the glomeruli, combined with less complete reabsorption of (the superfluous) water in the tubules. The plasma Cl falls to a slight extent, *e.g.* by about 6 per cent. This is due (i) mainly to salt passing out of the blood into the alimentary canal and into the tissue spaces to maintain proper osmotic relations there, and (ii) in part to slight dilution of the blood. As the diuresis passes off, the blood Cl rises again almost to normal. There is a brief initial washing out of Cl in the urine. During the rest of the period of diuresis, the amount of NaCl in the urine falls, *e.g.*, from 1·18 to 0·09 grm. per hour, and the percentage, *e.g.*, from 1·34 to 0·08 (cf. Fig. 108 A and B). It is observed how a very minute change in the composition of the blood produces great changes in the output of urine in the direction of restoring the blood to its normal state.

There is no increased excretion of PO_4 or creatinine during water diuresis. The urea output is slightly increased, but not more than twice. It is clear, therefore, that the urinary constituents are largely, though not entirely, independent of one another as regards their excretion (Ambard). The *total* amount of solids eliminated in 24 hours during which much water is drunk is approximately the same as in a day of complete abstinence from fluid. Though, as stated, there may be a slight temporary increased excretion of Cl and urea at the beginning of, or *during* the period of diuresis, it is compensated for by a lessened rate of excretion immediately after the diuresis is over (Adolph).

If *isotonic* saline of a composition resembling Locke's solution is taken slowly, it is found to be fairly palatable. If 3 litres are drunk in an hour, the maximum diuresis attained is only 300 c.cm. per hour. The urinary output remains above 100 c.cm. per hour for more than 24 hours. The hæmoglobin concentration may fall by 10 per cent., indicating that definite dilution of the blood has occurred. It is noteworthy that, in spite of this

[1] Priestley, *Journ. Physiol.*, 1921, vol. lv. p. 305; Adolph, *ibid.*, p. 114.

marked degree of dilution of the plasma proteins, only slight diuresis takes place; but when saline is injected *intravenously* marked diuresis occurs. Saline is therefore retained better if given by mouth or per rectum. The reason for the difference is not understood. Isotonic saline appears to be absorbed as a whole from the intestine, and is retained for a much longer time in the body and in the blood before the excess of water and salt are got rid of (cf. Fig. 108, D).

If *salt* is ingested dissolved in a minimum amount of water, it too is not rapidly eliminated. It is retained in the tissues, and water is also taken

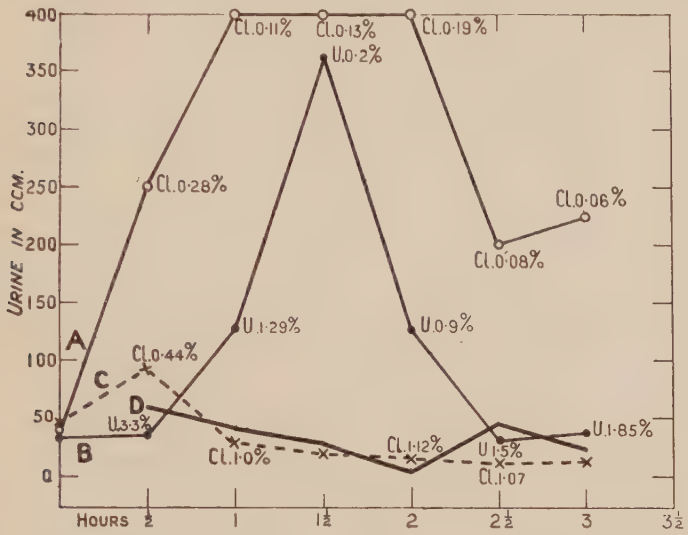

FIG. 108.—Chart of Urinary Output.

Ordinate = Volume of urine passed every half hour. Abscissa = Time in hours. A = Ingested 1760 c.cm. water on empty stomach. Note rapid onset of diuresis; about 1900 c.cm. urine passed in subsequent 3 hours. Cl (percentage chloride in urine) is low at the height of the diuresis and falls still lower at the end of the experiment, probably to compensate for earlier loss of Cl. B = Ingested 1180 c.cm. water after light lunch. Delayed onset of diuresis. U (urea percentage in urine) falls to 0·2 at height of diuresis (from initial level of 3·3) owing to large volume of urine passed. C = Ingested 1200 c.cm. water and received intramuscular injection of 0·5 c.cm. pituitrin. Diuresis was delayed for 4 hours in this case. D = Ingested 750 c.cm. Ringer-Locke's solution. No diuresis occurred.

up to maintain the appropriate osmotic relationship; the body weight is increased because of retention of saline. The excess fluid and salt are slowly eliminated in the course of a few days. If a person is given a *salt-free* diet, it is found that salt practically disappears from the urine, as it is all reabsorbed to maintain an adequate concentration of salt in the blood. If *caffeine* is now administered, salt reappears in the urine. It is suggested that caffeine paralyses reabsorption of salt by the tubules; more salt therefore remains in the tubules, exerts an osmotic pressure and so interferes with the reabsorption of water—diuresis therefore results. This may be the explanation of the diuretic action of caffeine, which should be particularly

of value in cases of renal œdema in which water and salt retention take place.

If there is excessive *loss* of fluid from the body by the bowel (*e.g.* diarrhœa), or by the skin because of excessive sweating, the flow of urine is correspondingly diminished. The blood becomes slightly concentrated, the plasma protein osmotic pressure rises, filtration in the glomeruli is diminished, there is a slower flow of fluid down the tubules, and more complete reabsorption of water takes place.

2. **Regulation of Blood Reaction.**—The way in which the kidney helps to regulate the *H ion concentration* of the blood has already been fully discussed (p. 224). Under normal conditions, the kidney may excrete the equivalent of 60 or 70 c.cm. of normal acid per day. The glomeruli filter a mixture of acid and basic phosphate which is slightly alkaline in reaction, the proportion of NaH_2PO_4 to Na_2HPO_4 in plasma being 1 : 4. The kidney eliminates the acid, while retaining the base as far as possible, and excretes NaH_2PO_4 and Na_2HPO_4 in the ratio of 9 : 1. The basic phosphate is changed into the acid form, and one molecule of base is retained in the body.

$$\underset{\text{Reabsorbed.}}{Na_2HPO_4} + H_2O = Na + OH + \underset{\text{Excreted.}}{NaH_2PO_4}.$$

The base may be absorbed as bicarbonate. When there is a tendency to *alkalæmia* the basic phosphate is eliminated, and bicarbonate as well, up to the limit of concentrating power of the kidney (p. 472).

3. **Rôle of the Pituitary Body.**—There is little doubt that the pituitary body normally controls the volume of urine secreted daily (p. 149). If pituitrin is added to the blood which is perfused through an isolated mammalian kidney, the amount of urine formed is lessened, and there is an increase both in the total amount and in the percentage of Cl in the urine. The diminished urinary output is accompanied by a *rise in the oxygen consumption* of the kidney—*i.e.* more work is being done in the absorption of larger quantities of water against osmotic resistance. Pituitrin probably acts directly on the epithelium of the tubules, *increasing the absorption of water*, and perhaps *diminishing the reabsorption* of salt. For action of pituitrin in normal man and in diabetes insipidus, see pp. 147, 149.

4. **Excretion of End Products of Protein Metabolism.**—These substances, *e.g.* urea, sulphate, uric acid, are all no-threshold or low threshold bodies. Light is thrown on the mechanism of their elimination by a study of the diuretic action of sulphate when given intravenously.

If a strong solution of *sodium sulphate* is injected intravenously, it produces an abundant diuresis which is greater than that which results from corresponding amounts of sodium chloride. The urinary flow remains at its maximum longer, and sinks more slowly, and reaches its normal level after many hours. At first the presence of sodium sulphate in the blood attracts water from the tissue spaces, and produces dilution of the plasma proteins. The diuresis persists, however, after the original blood volume has been restored.

A study of the Cl and SO_4 content of plasma and urine, after the injection

of equimolecular amounts of these substances intravenously, throws some light on what is occurring (Cushny) :

	Height of Diuresis.		Towards End of Diuresis.	
	Cl per cent.	SO_4 per cent.	Cl per cent.	SO_4 per cent.
Serum . .	0·547	0·259	0·493	0·191
Urine . .	0·372	0·546	0·094	2·0

(1) The initial dilution of the plasma proteins results in increased glomerular filtration and " flooding " of the tubules, so that much Cl and water escape. Some absorption of water is occurring (to the extent of about 50 per cent.), for the SO_4 in the urine is 0·546 per cent., compared with 0·259 per cent. in the plasma, *i.e.* it is concentrated twofold. Some Cl, too, is absorbed, for the urinary Cl is 0·372 per cent. and the serum Cl 0·547 per cent.

(2) When glomerular filtration is lessened as the plasma proteins return to their original concentration, it becomes still more evident that SO_4 and Cl are being treated very differently by the kidney. SO_4, which is a no-threshold body, continues to escape so long as any remains in the blood. During the course of the experiment its concentration falls from 0·259 to 0·191 per cent. The tubules are absorbing water better, for SO_4 is now concentrated tenfold—plasma SO_4 is 0·191 per cent., urinary SO_4 is 2·0 per cent. As much Cl was lost during the initial " flood," practically all the Cl in the glomerular filtrate is resorbed so as to maintain the proper level of plasma Cl. The urinary Cl is now only 0·094 per cent. compared with a plasma Cl of 0·493 per cent. The presence of a 2 per cent. sulphate solution in the tubule, by its osmotic action, prevents the absorption of the normal amount of water, which therefore escapes in the urine. The diuresis is prolonged, and goes on until all the SO_4 is gradually eliminated from the body. The essential results of this experiment may be summarized thus : the presence of an excess of sulphate in the blood results in an excess of this substance in the glomerular filtrate ; as sulphate is a no-threshold body it is not reabsorbed and its excretion continues until it is all eliminated. The presence of sulphate raises the osmotic pressure in the tubules and interferes with the absorption of water—*i.e.* sulphate causes water to be retained in the tubules for its own elimination. The sulphate is excreted without much loss of essential constituents of the plasma. This type of diuresis is known as *tubule diuresis*, because it is due to the presence in excess of a no-threshold substance in the tubules. The polyuria of diabetes mellitus is due to the same mechanism (p. 419)—the excess sugar acting as a no-threshold body. If protein is ingested, or if tissue breakdown takes place, no-threshold bodies are formed which are eliminated by the kidney in a manner similar to that just described.

The oxygen consumption of the kidney is said to be increased during SO_4 diuresis, *e.g.* from 0·4 to 0·9 c.cm. per grm. per minute. This cannot be readily explained. It may be due to the tubules doing more work absorbing

water against the great osmotic pressure of the urine (and perhaps to the active excretion of SO_4 as well).

5. **Urea Concentration.**—If water drinking is freely permitted and a varying protein diet is administered, it is found that the total amount of urea eliminated naturally varies. The *percentage* of urea in the urine is fairly constant.[1] If urea is injected intravenously or taken by the mouth, a varying degree of hydræmia is produced, but as a rule not much water is attracted into the blood from the tissue spaces. Following an initial diuresis to eliminate the excess water from the blood, it is found that the additional urea is eliminated in the usual concentration in the urine. This is the basis of MacLean's *urea concentration test.*

The bladder is emptied, and 15 grms. urea are given by the mouth in 100 c.cm. water. The bladder is emptied after one, two, and three hours. The first specimen may be dilute because of the diuresis induced. The second specimen should contain 2 per cent. urea or over. If more than 120 c.cm. are secreted in the second hour, the urea percentage in the third specimen is determined. If the kidney cannot concentrate urea to 2 per cent., it is evidence of definite functional disorder. Normal kidneys may concentrate to 4 per cent. or over.

MacLean regards this test as a more delicate indication of the functional state of the kidneys than determination of the blood urea. The blood urea is 20 mrgms. per cent. or less in young subjects, and 40 mrgms. or over in older people. Three-quarters of the total renal tissue must be removed before the blood urea rises in animals, *i.e.* a considerable renal lesion must be present before the blood urea rises. A high blood urea is not specific evidence of renal failure, and is found when there is excessive loss of fluid from the body (*e.g.* from sweating, diarrhœa), and in high intestinal obstruction (p. 410). The blood urea is also raised by a high protein diet.

6. **Concentration of Salts.**—The maximum concentration of urea by the kidney is independent of that of salts. It has been shown, however, that either chloride or bicarbonate separately can be concentrated to a maximum of 0·33 molar.[2] If bicarbonate is ingested after the maximum excretion of chloride is attained, the concentration of Cl in the urine *falls*, the sum of Cl and HCO_3 amounting to 0·33 molar. The concentration of phosphate, however, is independent of these two. Such inter-relations require further elucidation.

The *volume of urine* secreted depends on—(i) water ingested (p. 468); (ii) water lost by other channels (p. 470); (iii) protein in diet (p. 436), because of the urea and other nitrogenous bodies it gives rise to (p. 471); (iv) caffeine bodies in diet which have diuretic action (p. 469); (v) muscular activity and sleep (p. 463); (vi) emotion may increase the flow of urine but very often gives rise to *frequency* of micturition (p. 142).

Water Intoxication.—Patients with diabetes insipidus drink and excrete enormous amounts of water, up to 40 litres per day (cf. p. 149). If water is withheld from these patients, serious symptoms develop from the excessive loss of water in the urine—*i.e.* sunken facies, feeble pulse, fainting, etc. If the flow of urine is diminished by means of pituitrin without corre-

[1] The volume of urine passed will vary with the protein intake (see Table, p. 436).

[2] A *molar* solution is one which contains the molecular weight in grammes of the substance in 1 litre of water.

sponding limitation of the water intake, grave manifestations develop—*e.g.* headache, nausea, asthenia, inco-ordination of movement—from the excessive water content of the body. Experimentally, water in very large amounts may be given by the stomach tube to normal dogs. Retching, vomiting, and violent convulsions resembling those of strychnine poisoning occur at intervals, alternating with asthenia which borders on coma. Death frequently occurs in coma or in convulsions. If recovery takes place, the animal is normal within a few hours after the administration of water is stopped. A condition of subacute poisoning can be induced in rabbits by giving daily, over a long period, an amount of water equal to the body weight. Post mortem few changes are found, but the most significant is œdema round the vessels of the brain. The intracranial pressure is definitely raised. This can be prevented as usual (cf. p. 7) by intravenous injection of hypertonic saline. The symptoms described are attributed to the rise of pressure within the skull cavity (Larson, Weir, and Rowntree). These observations are of importance in relation to the explanation of *uræmic* manifestations.

Nephritis.—In *acute* nephritis the whole kidney is thrown out of action. Water, salt, the nitrogenous bodies, and acids are all retained in the blood. The volume of the urine is reduced to a few ounces daily, and it contains protein, blood, and casts. The blood pressure is raised—*e.g.* systolic blood pressure, 180 mm. Hg; diastolic, 110 mm. There is a rise in the urea and non-protein nitrogen of the blood. As salt and water are retained there is œdema (p. 307), increased volume and dilution of the blood as indicated by the fall in hæmoglobin percentage. The hydræmia may contribute to the raised blood pressure. When recovery sets in, it is marked by an increase in the flow of urine; polyuria may be present for a short time owing to the high blood pressure, the raised blood urea which acts as a diuretic, and the excess fluid in the blood. Later the œdema and hydræmia subside and the blood pressure returns to normal. In the recovery stage, three to four times the amount of nitrogen present in the diet may be excreted in the urine for a few days.

Two main varieties of *chronic* nephritis may be recognized: (i) The *azotæmic* form (chronic glomerulo-nephritis), in which the nitrogenous waste products are not adequately eliminated and are retained in excess in the blood. (ii) Lipoid nephrosis (chronic parenchymatous nephritis), in which there is retention of water and salt in the tissues (p. 307). The main features of these two forms of renal disease are summarized in the following table (modified from MacLean):

Azotæmic Nephritis.	Lipoid Nephrosis.
Œdema absent.	Marked œdema present (p. 307).
Protein usually present in the urine, but often slight or moderate in amount.	Protein present in the urine, usually in large amounts (p. 308).
Urea concentration in the urine diminished.	Urea concentration normal.
Tendency to increase of urea and other nitrogenous products in blood.	No nitrogen or chloride retention in blood. Blood cholesterol markedly raised (p. 394).
Cardio-vascular changes marked (*i.e.* enlarged heart, thickened arteries, raised blood pressure).	Cardio-vascular changes slight.
Tendency to uræmia.	Little tendency to uræmia.

Uræmia.—Two varieties of uræmia are usually recognized: (1) *latent* (or asthenic) and (2) *sthenic.*

(1) Latent uræmia after obstruction of both ureters or of the renal tubules (p. 183), or after removal of both kidneys. There is loss of appetite, progressive weakness, increasing stupor, coma, and death finally results in about a week. As may be expected, there is a very marked increase in the nitrogenous constituents of the blood; for example, the blood urea may exceed 0.9 per cent. It must particularly be noted that this condition is not associated with a rise of blood pressure; there is no irritation of the cortical centres or convulsions. It has also been shown experimentally that after double nephrectomy no acidæmia develops. It is claimed by some workers that if urea is administered to normal subjects in such amounts that the concentration of this substance in the blood is raised to 160 mgrms. per 100 c.cm. symptoms resembling those of latent uræmia may develop.

(2) *Sthenic* uræmia occurs in the course of various forms of Bright's disease, especially acute or chronic glomerulo-nephritis. It is characterized by epileptiform convulsions, markedly raised blood pressure, gastro-intestinal disturbances, and dyspnœa.

(i) As pointed out (p. 473) the symptoms of water intoxication resemble closely the manifestations of uræmia. Cerebral œdema and raised intracranial pressure may possibly be responsible for the headache, vomiting, loss of sight (amaurosis), the convulsive movements, and the coma. When lumbar puncture is carried out, the cerebro-spinal fluid is found to be under increased pressure; after the excess fluid has been removed temporary improvement may result. The hypertension may in part be due to the raised intracranial pressure; it would then be a compensatory phenomenon, *i.e.* an attempt to maintain an adequate cerebral circulation.

(ii) Most cases of uræmia (though exceptions are met with) show an increase of the non-protein nitrogen from the normal level of 25 to 40 mgrms. per 100 c.cm. to 50,100, or 300 mgrms. The blood urea may be 200 mgrms., the uric acid 5 to 10 mgrms., and the creatinine 2 to 40 mgrms. As previously indicated the convulsions and the hypertension cannot be attributed to nitrogenous retention. An increase in the blood phosphate and a fall in the serum calcium (to 6 mgrms.) have been noted in some cases; the increased excitability of the nervous system may be analogous to tetany (cf. p. 162) and be due to a disturbance of the balance between the different ions of the blood.

(iii) Foster claims that a crystalline substance can be isolated from the blood of uræmic patients who are showing convulsions, which cannot be detected in normal blood or in the blood in any diseased state except uræmia of this type. He states that injection of this body into animals produces convulsions and death. This work (if confirmed) suggests that a poisonous substance may result from a wholly abnormal type of metabolism, and be in part responsible for the epileptiform seizures, paralyses, etc.

(iv) In some cases of uræmia there is a definite rise in the H ion concentration of the blood. This may produce great hyperpnœa and a fall in the alveolar and arterial CO_2 tension (p. 227). The acidæmia, which may in part be due to failure of the kidney to eliminate the acid phosphate, may give rise to convulsions and coma, and still further damage the renal tissue.

If alkali is given in sufficient doses to restore the normal blood reaction, the convulsions may cease, consciousness is restored, and there is improved renal function, as shown by a diminished amount of albumin and casts in the urine. The improvement is only temporary.

(v) As a result of the poisoned and depressed condition of the respiratory centre, Cheyne-Stokes breathing (p. 327) and paroxysmal dyspnœa (p. 372), especially at night, may be present.

(vi) Vomiting and diarrhœa are common. Vomiting may in part be of cerebral origin. Both disturbances may be due to irritation of the mucous membrane of the bowel from the excretion into it of a poisonous body. Ulceration of the bowel (colon, lower ileum) is often present, and may be associated with bloody stools.

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